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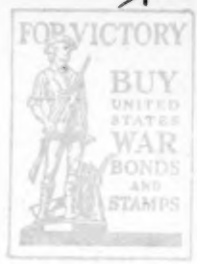

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THE TREATMENT OF BACTERIAL ENDOCARDITIS WITH PENICILLIN

Experiences at the Boston City Hospital During 1944*

MANSON MEADS, M.D.,† H. WILLIAM HARRIS, M.D.,‡ AND MAXWELL FINLAND, M.D.§
WITH THE TECHNICAL ASSISTANCE OF CLARE WILCOX

BOSTON

FLEMING,[1] in his original studies on the antibacterial action of cultures of his strain of Penicillium, included some strains of *Streptococcus viridans*, which he found to vary considerably in their susceptibility. Others[2–8] have since confirmed these findings with more purified preparations of penicillin in vitro, noting the wide differences in susceptibility of single strains and finding some to be relatively resistant. Clinical trials in the treatment of subacute bacterial endocarditis were begun in 1942. The earliest reports were somewhat discouraging,[9–16] but they did suggest the possibility that larger doses of penicillin given over a longer time might produce better results. Although negative blood cultures were usually obtained for brief periods during the administration of the small doses, bacteremia recurred after the treatment was ended.[9, 11, 12, 14]

Loewe and his associates,[17] early in 1944, reported favorable results in 7 consecutive cases of subacute bacterial endocarditis with combined heparin and penicillin treatment, but their cases had been followed for only a short time when this report was made. Later in the year, as larger amounts of penicillin became available, additional encouraging reports began to appear.[18, 19]

In this paper are presented the findings in 9 cases of subacute bacterial endocarditis caused by *Str. viridans* and in 7 proved or probable cases of acute bacterial endocarditis due to other organisms, all of which were treated with sodium penicillin at the Boston City Hospital during 1944. The final evaluation of the results in surviving cases must, of course, depend on observations of a larger number of cases followed for a considerably longer period. The purpose of this presentation is to bring out some of the problems encountered during the treatment and in the immediately ensuing period. For convenience the cases will be considered according to their bacterial etiology, but the features are shown together for all the cases in the accompanying tables, and the relevant findings in single cases appear in the text figures.

CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

Patients and methods. The 9 patients included in this study represent consecutive, unselected but typical cases of subacute bacterial endocarditis admitted to the medical wards of the Boston City Hospital between February and October, 1944. The diagnosis was based on the finding of multiple positive blood cultures, embolic manifestations and evidence of valvular heart disease. The patients ranged in age between nineteen and fifty-seven years; 5 were under thirty and 4 were over forty. Five were females and 4 were males. All had received courses of one or more of the sulfonamides without benefit before penicillin was started, but sulfonamides were not used during the penicillin treatment. They were sometimes given later for special indications.

Penicillin treatment was begun only after multiple positive blood cultures had been obtained. It was usually given by repeated intramuscular injections and only occasionally by constant intravenous infusion in either 0.85 per cent sodium chloride or 5 per cent glucose solution in water, using a total of 1500 to 2000 cc. per day. A predetermined dosage was used to start the treatment, usually 25,000 units every two hours intramuscularly, but this was altered later according to the clinical response or the serum concentrations obtained.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

Presented, in part, at a meeting of the New England Heart Association, Boston, November 20, 1944.

Most of the penicillin used in this study was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

†Research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory.

‡Research fellow, Thorndike Memorial Laboratory.

§Assistant professor of medicine, Harvard Medical School; chief, Fourth Medical Service, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

The organisms varied in their rate of growth in blood cultures and in subcultures. They were characteristic strains of *Str. viridans* that failed to react with serums of the Lancefield Groups A, B, C, D and G.* The organisms were tested for their sensitivity to penicillin by the method of Rammelkamp and Maxon,[20] modified in later tests only by the use of 0.5-cc. amounts of broth for making the penicillin dilutions. The concentrations of penicillin in the serum were determined by the serial dilution method of Rammelkamp.[21] From three to seventeen positive blood cultures, with an average of seven, were obtained in each case before penicillin treatment was begun.

Blood cultures were also taken at frequent intervals early in the course of the penicillin treatment and then twice weekly until discharge. Further blood cultures were taken during follow-up examinations. In the latter part of the study, penicillinase† was added to the culture medium when blood was obtained for culture during penicillin therapy.

Heparin was given to 3 of the patients by continuous intravenous infusion. The amount was adjusted in an attempt to keep the blood clotting time at about 60 minutes (range, 30 to 120 minutes).‡ This usually required about 200 to 250 mg. daily. Heparin was discontinued when hemorrhages or other untoward reactions occurred.

Some of the highlights of the clinical course, the treatment and the laboratory findings in the individual cases are shown in Figures 1 to 9.

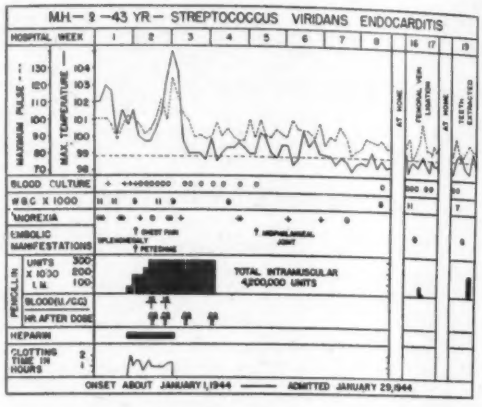

FIGURE 1. *Case 1.*

The patient began to improve soon after treatment with heparin and penicillin was started. The marked rise in temperature after a week of treatment was accompanied by malaise, anorexia, nausea and abdominal discomfort. Fever and symptoms subsided within a few hours after heparin was stopped. During each of two subsequent admissions she had a short course of penicillin; the first was given before and after femoral-vein ligations for thrombophlebitis, and the second was given before and after extraction of infected teeth.

Duration before treatment. Some of the relevant dates in each of the cases are listed in Table 1. The

TABLE 1. *Significant Dates.*

Case No.	Age	Sex	Date of Hospital Entry	Date of First Symptom	Date Penicillin Begun	Date When Afebrile	Date Last Seen
	yr.						
1	43	F	Jan. 29	Jan. 1	Feb. 4	Feb. 13	Dec. 15
2	29	F	Mar. 1	Jan. 25	Mar. 11	Mar. 13	Nov. 15
3	40	M	Apr. 24	Mar. 10	May 3	May 13	Nov. 15
4	20	F	May 27	May 20	June 5	June 19	Nov. 15
5	19	F	July 20	July 1	July 25	July 26	Nov. 15
6†	25	M	Oct. 17	May 1*	Oct. 25	Oct. 26	Dec. 1
7‡ (*a*)	57	M	Apr. 17	Feb. 9	May 8	May 10	
(*b*)			Oct. 27	Sept. 25	Oct. 30	Nov. 4	Dec. 15
8§	49	M	Dec. 16*	Oct. 15*	Feb. 4	Feb. 14	May 17 (died)
9	21	F	May 8	Apr. 25	May 16	Died	May 25
10	35	M	Feb. 6	Jan. 28	Feb. 21	Mar. 4	Nov. 22
11	65	M	Jan. 19	Jan. 17	Mar. 14	Mar. 15	Nov. 15
12	55	M	Jan. 30	Jan. 24	Feb. 4	Died	Feb. 11
13	34	F	Apr. 8	Mar. 25	Apr. 15	Apr. 19	Nov. 25
14	73	M	Apr. 14	Not known	Apr. 21	Died	Apr. 21
15	20	F	Apr. 15	Mar. 25	Apr. 28	Died	May 1
16	52	M	Oct. 28	Oct. 26	Oct. 28	Died	Nov. 13

*1943 (all others 1944).
†Patient readmitted for a recurrence.
‡Two admissions, indicated as (*a*) and (*b*).
§Patient died during a readmission for cardiac failure.

The patients were examined daily during treatment and at frequent intervals thereafter for evidence of embolic phenomena, changes in cardiac murmurs and other complications.

time of onset of symptoms as given by the patient is necessarily only approximate, and there is reason to believe that the disease was active in most cases for a longer period. The duration of symptoms of active infection at the time of admission to the hospital was five weeks or less in 6 of the cases, about two months in 2 cases and almost one and a half years in Case 6. Treatment with penicillin was started within ten days after entry of 7 of the cases,

*We are indebted to Miss Ruth M. Drew of the Department of Bacteriology and Immunology, Harvard Medical School, for the streptococcus groupings and typings.

†Supplied by Drs. H. J. White and R. O. Roblin, Jr., of the Stamford Laboratories, American Cyanamid Company.

‡The heparin administration and blood studies in these cases were carried out by Drs. C. S. Davidson and John H. Freed.

after three weeks in Case 7, and after seven weeks in Case 8. Recurrences occurred in Cases 6 and 7; these will be considered separately.

Sensitivity of the organisms. Data concerning the organisms obtained from the blood cultures are shown in Table 2. The strains of *Str. viridans* varied in their sensitivity to penicillin, the M. I. C. (minimum inhibiting concentration) ranging from 0.011 to 0.031 Oxford units per cubic centimeter of culture containing 1000 to 10,000 streptococci. Some of the organisms were tested several times with results varying twofold in either direction on different occasions.

Penicillin dosage. The dose most often used was 25,000 units intramuscularly every two hours. Variations from this dosage were made either for the purpose of observing the clinical and bacteriologic response to smaller doses, or because the clinical response was inadequate, or when the serum concentration could not be maintained above the M. I. C. for the patient's strain. Attempts were made to achieve the desired effect in some of the patients by giving hourly intramuscular doses, in others by constant intravenous infusions and, in some patients who were in congestive failure, by reducing the fluid intake. The actual amounts of penicillin given are shown in Table 3. Treatment was continued for twelve to nineteen days except in Case 9, in which death occurred on the seventh day after almost 2,000,000 units had been given. The total amount used in the remaining cases varied

TABLE 2. *Results of Blood Cultures.*

Case No.	No. of Cultures Positive before Penicillin	Organism	M. I. C. (Penicillin Sensitivity*)	Time after Beginning of Therapy — Last Positive	Time after Beginning of Therapy — First Negative
				hr.	*hr.*
1	3	*Str. viridans*	0.016	16	18
2	4	*Str. viridans*	0.022	0	4½
3	5	*Str. viridans*	0.031	72	120
4	8	*Str. viridans*	0.031	21	30
5	4	*Str. viridans*	0.031	48	72
6	6	*Str. viridans*	0.031	6	8
7 (*a*)	9	*Str. viridans*	0.031	2	4
(*b*)	1	*Str. viridans*	0.008	48 (before)†	0
8	17	*Str. viridans*	0.011	24	48
9	9	*Str. viridans*	0.022	Post-mortem	—
10	9	Type 7, pneumococcus	0.011	0	4
11	3	Type 5, pneumococcus	0.011	0	3½
12	6	Type 6, pneumococcus	0.011	4	8
13	6	Str. haemolyticus (Group A, Type 28)	0.008	0	24
14	1	Str. haemolyticus (Group A)	0.008	Post-mortem	—
15	4	Gonococcus	—	48 (before)‡	48 (before)
16	1	*Staph. aureus*	0.031	24	120

*Units of penicillin added to 1 cc. of culture (containing 1000 to 10,000 organisms) that gives no growth in 24 hours.
†The only positive culture during the relapse was obtained 48 hours before the second course of penicillin was started.
‡Blood cultures became negative after treatment with sulfamerazine and 48 hours before penicillin was begun.

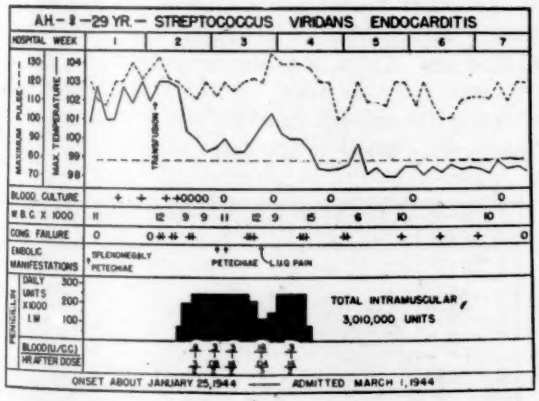

FIGURE 2. *Case 2.*

Shortly before penicillin therapy was started the patient developed congestive failure, which increased during the course of the treatment. She subsequently regained compensation and no longer requires digitalis. Adequate blood concentrations were maintained with small doses in this case.

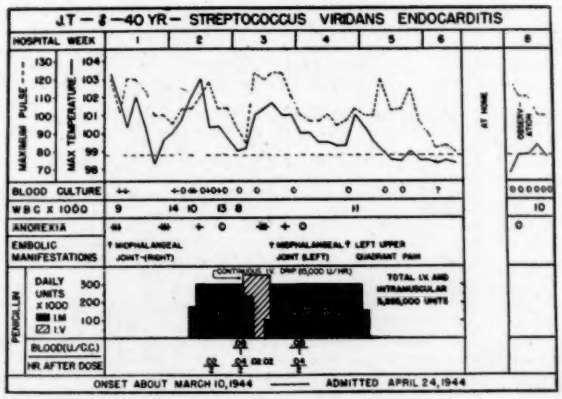

FIGURE 3. *Case 3.*

Because bacteriostatic levels were not regularly maintained for two hours after 25,000 units intramuscularly the patient was given penicillin by constant intravenous drip at the rate of 15,000 units per hour for three days. During this time there was a return of fever and the intramuscular method was resumed. The patient was readmitted for further observations because of contaminants grown in the last blood culture obtained before discharge. No evidence of a recurrence of infection was found.

from 3,000,000 to 6,000,000 units except in Cases 6 and 7, in both of which a total of more than 9,000,000 units was given in two separate courses.

Heparin. This drug was used in Cases 1, 4 and 8. In Cases 1 and 4 it was discontinued after eight and twelve days, respectively, because of the occurrence of a rising temperature and pulse rate associated with malaise, sweating, anorexia, nausea, drowsiness and irritability. All these symptoms completely subsided within twelve hours after the heparin was stopped. It was therefore assumed that these findings represented an untoward reaction or sensitization to heparin similar to drug fever or serum sickness. In Case 8, the heparin administration was stopped on the fifth day, after the sudden occurrence of hemiparesis associated with grossly bloody cerebrospinal fluid.

TABLE 3. *Summary of Therapy.*

CASE NO.	PENICILLIN THERAPY* SIZE OF DOSE	INTERVAL	NO. OF DOSES	TOTAL DOSAGE	DURATION	DURATION OF HEPARIN THERAPY
	units x 10³	*hr.*		*units x 10³*	*days*	*days*
1	15	2	35	4200	16	8
	25	2	147			
2	15	2	10	3010	14	—
	20	2	88			
	15	3	16			
	20	2	43			
3	25	2	76	5895	19	—
	360					
	25	2	127			
4	15	2	30	5550	19	12
	10	1	58			
	15	1	177			
	25	2	84			
	25	2	35	3555	13	—
	20	2	134			
6	25	2	60	3700	14	—
	20	2	110			
7(*a*)	25	2	37	4225	12½	—
	15	1	220			
(*b*)	25	2	112	5100	15	—
	20	1	46			
	15	1	92			
8	15	2	35	4200	16	5
	25	2	147			
9	25	2	74	1865	6	—
10	15	2	219	3285	18	21
11	15	2	48	975	6	—
12	15	2	36	1840	7	7
	25	2	52			
13	100			1455	14	—
	15	3	77			
14	15	3	2	30	¼	—
15	15	3	22	330	3	—
16	15	2	5	3820	16	—
	15	3	21			
	20	2	172			

Notes:

Case 2. Levels on 3-hourly dosage adequate during congestive failure.
Case 3. Levels were inadequate during intravenous therapy and symptoms recurred.
Case 4. Patient given 20,000 units every 2 hours for 3 days after a splenic infarct, which occurred 16 days after the main course of penicillin.
Case 5. Patient weighed 90 lb.; blood levels were adequate on lower doses.
Case 6. Best clinical response; bacteriostatic levels only for 1 hour after injection.
Case 7. Recurrence (positive blood culture and chills) after 5½ months.
Case 8. Penicillin given intrathecally for 3 days because of pleocytosis and organisms seen (cultures negative) in spinal fluid during hemiparesis.
Case 11. Intrathecal doses for 6 days for meningitis.
Case 12. Intrathecal doses last 4 days for meningitis.
Case 16. Intrathecal doses during first 10 days for meningitis.

*All injections were given intramuscularly in the order noted, with two exceptions, the second series in Case 3 and the first in Case 13 (in each, the figure is the daily intravenous dose, which was continued for 3 days).

Effect of penicillin on the symptoms and signs of infection. The clinical course in those who did not have serious complications was marked by an increase in appetite, a decrease in irritability and sweating and a general feeling of well-being, which began twenty-four to forty-eight hours after the penicillin was started. In 4 of the cases, the fever subsided, with the oral temperature dropping and remaining below 100°F., within forty-eight hours, whereas in the other 4, excluding Case 9, some fever continued during nine to fourteen days of treatment (Table 1). There was an occasional rise in temperature later in some of the cases, either associated with embolic manifestations or arising from causes not related to the major illness.

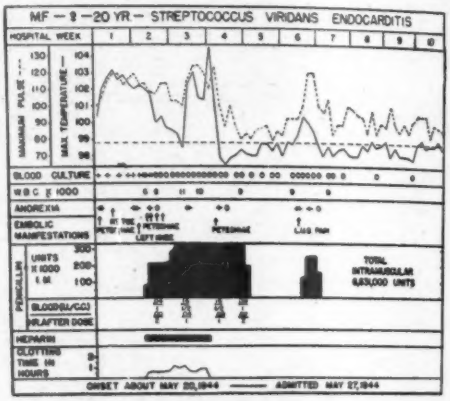

FIGURE 4. *Case 4.*

In this case, small doses of penicillin were used during the first five days but they were later increased. The marked rise in temperature lasting about four days was accompanied by vague discomforts, all of which subsided, together with the fever, promptly after the heparin was discontinued. A second course of penicillin was given for three days following the occurrence of a splenic infarct and fever eleven days after the first course was completed.

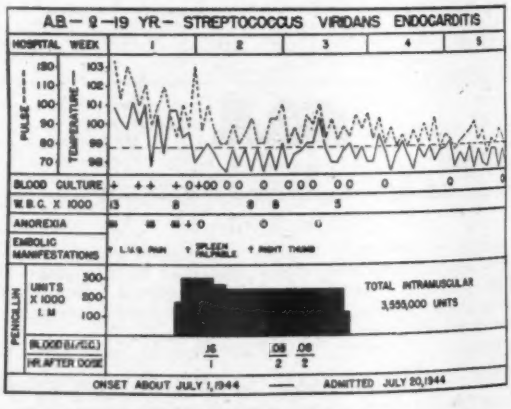

FIGURE 5. *Case 5.*

The patient weighed only about 90 pounds, and high levels were maintained on doses of 20,000 units every two hours.

The white-cell counts were only slightly elevated in most cases, and the effect of treatment was variable. The erythrocyte sedimentation rates like-

wise varied. In each of the recovered cases, however, these findings were normal before the patient left the hospital. The hemoglobin and red-cell counts likewise returned to normal except in Case 6, which will be referred to later.

Enlargement of the spleen was noted before treatment was begun in 4 cases (Cases 1, 2, 5 and 6), and

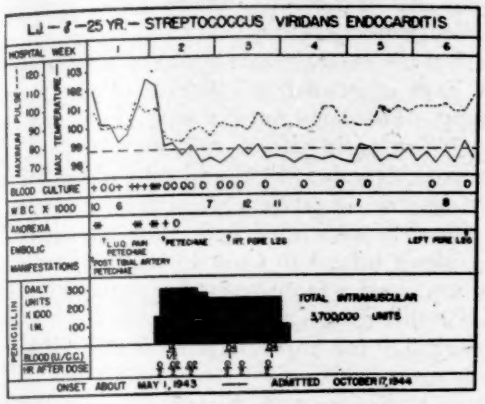

FIGURE 6. *Case 6.*

The patient had symptoms of active infection for about one and a half years before admission to the hospital. He improved rapidly after penicillin was started, although adequate blood levels were not maintained in his blood. Before discharge he had evidence of embolism to the leg, and four weeks later he had a recurrence of symptoms of active infection and a positive blood culture. He was readmitted and again improved on penicillin but more slowly than previously.

there was tenderness over the spleen in 2 of them. The spleen remained palpable throughout most of

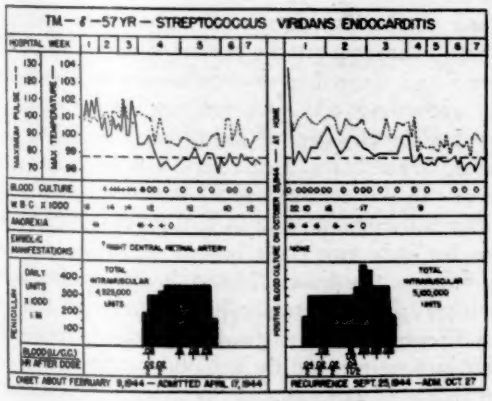
TM. — ♂ — 57 YR. — STREPTOCOCCUS VIRIDANS ENDOCARDITIS
HOSPITAL WEEK
MAXIMUM PULSE
MAX. TEMPERATURE
BLOOD CULTURE
W.B.C. X 1000
ANOREXIA
EMBOLIC MANIFESTATIONS
PENICILLIN
DAILY UNITS X 1000 I.M.
BLOOD (U./C.C.) HR. AFTER DOSE
POSITIVE BLOOD CULTURE ON OCTOBER 15, 1944 — AT HOME
ONSET ABOUT FEBRUARY — ADMITTED APRIL 17, 1944
RECURRENCE SEPT. 25, 1944 — ADM. OCT. 27

FIGURE 7. *Case 7.*

In this case it was not possible to maintain adequate levels with 25,000 units every two hours and the dosage was changed to 15,000 units every hour. There was a recurrence of symptoms, and a single positive blood culture was obtained after four and a half months. A second course of penicillin was then given in spite of the fact that other blood cultures were negative. The patient again showed a good clinical response to the treatment.

the course of treatment in these 4 cases, but receded later and was no longer palpable at the time of the last examination in any of the living patients. In no case was enlargement of the spleen seen for the first time after the treatment was started.

Effect on bacteremia. Data indicating the effect of penicillin treatment on the results of blood cultures are shown in Table 2. The numbers of positive cultures obtained in each case before treatment was

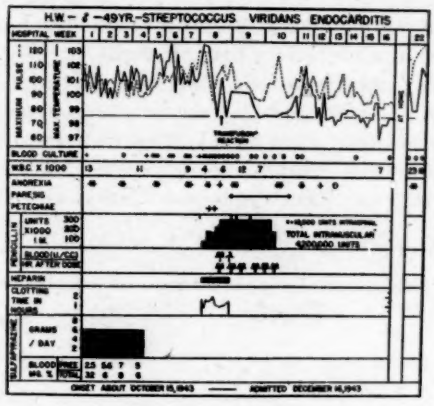

FIGURE 8. *Case 8.*

Adequate levels were readily maintained in this case, and the patient improved soon after treatment with heparin and penicillin was started. On the fifth day of treatment the patient became comatose and developed hemiparesis. The cerebrospinal fluid was bloody and showed organisms on smear that could not be cultured. Heparin was discontinued, and three intraspinal injections of penicillin were given. The patient recovered from this episode and improved steadily but continued to have poor cardiac function. He died three and a half months later in what seemed to be so-called "forward failure." At autopsy there was healing of the remnants of vegetations on the aortic valve; occasional organisms were seen in the smears of the ground-up vegetations, but cultures yielded no growth. There was a large splenic abscess, from which Streptococcus viridans *was grown.*

begun are also listed. The last positive culture was obtained before the first dose in Case 2 and from two to seventy-two hours after treatment was begun in the remaining cases except Case 9, in which the cardiac blood obtained at autopsy was positive in

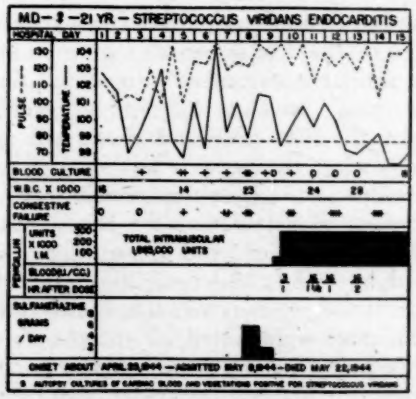

FIGURE 9. *Case 9.*

The patient had had symptoms for only three weeks and had developed severe congestive failure before treatment with penicillin was started. Although high blood concentrations were readily maintained, the patient died after seven days of the treatment, and Streptococcus viridans *was grown from the cardiac blood and vegetations.*

spite of more than six days of treatment. Subsequent blood cultures in the living cases were all

negative except during the recurrences in Cases 6 and 7. In 3 of the cases the blood cultures were negative in four to eight hours and in a fourth case within 18 hours after the initial dose of penicillin. The heart blood obtained at autopsy in Case 8 was sterile in spite of the fact that no penicillin had been given for the preceding three months.

Embolic manifestations. Signs and symptoms interpreted as evidence of embolic phenomena of one form or another were noted in each of the nine patients with *Str. viridans* endocarditis before treatment with penicillin was begun (Table 4). In most

TABLE 4. *Occurrence of Embolic Manifestations in Relation to Penicillin Therapy.*

CASE NO.	BEFORE THERAPY	DURING THERAPY	AFTER THERAPY
1	+	+*†	+
2	+	+	0
3	+	+	0
4	+	+*‡	+
5	+	+	0
6	+	+	+
7 (*a*)	+	0	0
(*b*)	0	0	0
8	+	+*	0
9	+	0	–
10	+	0	0
11	+	0	0
12	+	+*	–
13	0	0	0
14	+	0	–
15	+	0	–
16	+	0	–

*Embolic manifestations occurred during treatment with heparin.

†Positive blood culture obtained at the time when the embolic manifestations were observed (in the remaining cases, all blood cultures taken when emboli occurred during or after penicillin treatment showed no growth).

‡Embolic phenomena occurred after heparin had been discontinued.

of the cases there were multiple manifestations. Lesions of the extremities, including the joints, were noted in 7 cases, splenic infarction in 4, hematuria in 3, crops of petechiae in 3, occlusion of the central retinal artery in 1, and a pulmonary infarct in 1.

In each of the 3 patients who were treated with heparin, similar occurrences were noted during its administration. In Case 1, crops of petechiae appeared for the first time and chest pain occurred on the day after the heparin was started. A blood culture taken at the time was positive. In Case 4, several crops of petechiae were noted during the heparin administration, and again after it was discontinued but while the penicillin was still being given. In this case many blood cultures taken when these petechiae were noted all showed no growth. In Case 8, a few petechiae were noted for the first time during the heparin treatment, and on the fifth day of this therapy the patient became comatose and developed a hemiparesis. A lumbar puncture done at that time yielded cerebrospinal fluid that was grossly bloody and showed typical short chains of gram-positive cocci in the smear, but culture of the fluid gave no growth. Penicillin was nevertheless given intrathecally in 10,000-unit doses after each of three lumbar punctures.

At first it was thought that these phenomena were associated with the heparin administration, but similar ones occurred in 4 other patients during treatment with penicillin alone. Crops of petechiae were noted during the penicillin therapy in Cases 2 and 6, splenic infarcts, with pain and tenderness in the left upper quadrant, in Cases 2, 3 and 5 and lesions of the joints and extremities in Cases 3, 5 and 6. All the blood cultures taken when these occurred were negative.

In 3 of the cases, lesions occurred in seven to fourteen days after the completion of the penicillin therapy. These involved a finger joint in Case 1, the left foreleg in Case 6 and the spleen in Case 4. In these cases also, all the blood cultures taken at the time were negative. Slight fever, anorexia and malaise were associated with these manifestations. The splenic infarct in Case 4 occurred after a large splenic abscess was discovered at autopsy in Case 8, and for this reason the patient was given a course of penicillin for three days — 20,000 units every two hours.

Cardiac findings. A history of previous rheumatic fever was obtained in 6 cases (Table 5). The other 3 patients were aware of having cardiac murmurs for six to twenty-three years, although they had had no previous rheumatic manifestations. Clinically, the mitral valve alone was considered to be involved in 4 cases and both the mitral and aortic valves in the other 5. In 2 of the former, there was no evidence of stenosis, that is, only a systolic murmur was heard, — whereas in 1 of the latter (Case 8), only the aortic valve was found to be involved at autopsy.

Two of the patients were apparently well compensated throughout the period of observation. The other 7 had some degree of failure, which was classified, according to *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*,[22] as Grade II in 4 cases, Grade III in 1 case, and Grade IV in 2 cases. One of the patients (Case 8) had been taking digitalis for a long time, and in 2 other cases it had been given for only two days before penicillin treatment was begun. In Cases 2 and 9, congestive failure was increasing progressively just prior to the penicillin therapy, and in the former case this was apparently precipitated by a blood transfusion.

In this group of cases of *Str. viridans* endocarditis, the development of congestive failure during or soon after the course of penicillin did not occur. Failure was aggravated in some cases, but the cardiac status remained essentially unchanged in most cases. In Case 2, there was decided improvement during convalescence, and the patient since leaving the hospital has been able to carry on considerable activity without dyspnea or edema. One patient (Case 8) who had marked aortic insufficiency died three months after the penicillin treatment with marked failure but without any evidence of pulmonary or peripheral congestion.

Recurrences or possible reinfections. Thus far there has been a recurrence of symptoms and of bacteremia in 2 cases. Case 7 was one in which, because of the failure to maintain bacteriostatic levels throughout the two-hour period after an intramuscular dose of 25,000 units, the patient was given 15,000 units every hour; he seemed to improve following this change. Four months after the treatment was stopped the patient had a recurrence of the original symptoms, and a single positive blood culture was obtained four weeks later. Other blood cultures both before and after this positive one were negative. The patient was nevertheless given another course of penicillin, with rapid alleviation of the symptoms. Interestingly enough, the organism obtained during the recurrence grew more slowly, had a somewhat different colony morphology and, in parallel tests, was more sensitive to penicillin than the one obtained originally (Table 2). No peripheral embolic manifestations were seen during this recurrence.

Another patient (Case 6) was recently readmitted. One week after his discharge from the hospital, he developed a cold with coryza and headache and a few days later again had chills, fever and sweats. New crops of petechiae appeared on the trunk, and there were several tender nodular lesions on the fingers and toes. Several positive blood cultures were obtained, but in this case the organisms had about the same sensitivity to penicillin as those obtained originally, although they too grew somewhat more slowly and in smaller colonies. The symptomatic response to the second course of penicillin was not nearly so striking as that to the initial course. The patient became bacteria-free after fifteen hours and improved symptomatically after three days of treatment.

Complications. There were no untoward reactions to the penicillin except for the temporary local discomfort of the injections. Besides the embolic manifestations the only significant complication was the occurrence of thrombophlebitis of the legs in 2 patients. Interestingly enough, one of these patients received heparin through an arm vein, and in both cases the penicillin was given entirely by intramuscular injection. In Case 1, swelling and pain in one leg began before the patient left the hospital. She was readmitted and had a bilateral femoral ligation because of increasing edema and discomfort, and was given a few doses of penicillin before and after the operation. She was subsequently readmitted for extraction of teeth and was again given penicillin before and for twenty-four hours after this procedure. The other patient (Case 7) developed pain and tenderness in the popliteal region with a rise in fever before the completion of the second course of penicillin. This all cleared without special treatment. In Case 6, there was a thrombophlebitis at the site of the constant intravenous infusion during the second course of treatment.

Fatal cases. Two of the 9 patients died, one (Case 9) after only six days of treatment and the other (Case 8) three months after the treatment was completed (Table 6). The former had marked congestive failure, which remained unaffected by treatment with penicillin and digitalis. In this case it was possible to maintain high levels, well above the M. I. C. for the patient's own strain, throughout the two-hour interval between doses. Blood cultures taken after the second day of penicillin were negative, but a culture of the cardiac blood at autopsy was positive, and the organisms were seen in smears and grown in cultures of the large vegetation that was found on the aortic valve.

TABLE 5. *Cardiac Findings.*

CASE NO.	HISTORY OF RHEUMATIC INFECTION*	VALVES INVOLVED CLINICALLY	CARDIAC STATUS BEFORE THERAPY *Grade*	CARDIAC STATUS DURING PENICILLIN *Grade*	CARDIAC STATUS AT LAST OBSERVATION *Grade*
1	+	Mitral and aortic	II	II	II
2	+	Mitral	IV	IV	I
3	0 (23)*	Mitral	II	II	II
4	+	Mitral and aortic	I	I	I
5	+	Mitral	I	I	I
6	+	Mitral and aortic	II	II	II
7 (*a*)	0 (14)*	Mitral	II	II	
(*b*)		Mitral	II	II	II
8	0 (6)*	Mitral and aortic	III	III	Dead
9	+	Mitral and aortic	IV	IV	Dead
10	+	Mitral	I	I	I
11	0	None	I	I	I
12	0	Aortic	IV	IV	Dead
13	0	Aortic	III	IV	I
14	?	None	I	I	Dead
15	0	Aortic	I	IV	Dead
16	0	None	I	IV	Dead

*In 3 cases with no history of rheumatic infection, the figures represent the number of years that the patient had been aware of having a cardiac murmur.

In Case 8, infection was apparently controlled, but the patient did not regain compensation and continued to be weak and drowsy. He died a few days after re-entry to the hospital. A markedly hypertrophied and dilated heart was found at autopsy with small healing stumps of vegetations on the aortic valve. Smears of these vegetations showed rare organisms, but cultures were negative. There was a large abscess in the spleen, and a culture of pus from it yielded *Str. viridans*. The sensitivity of this strain to penicillin was the same as of that originally obtained from the blood.

One additional fatal case should be briefly mentioned. In this case the data are not shown in the tables. The patient was a man of fifty-three who had had symptoms of infection with changing murmurs but no embolic phenomena for two months before penicillin was begun. He had received sulfonamides without benefit and had three positive blood cultures for *Str. viridans* after this treatment was stopped. He had a systolic murmur at entry and developed a mitral diastolic murmur and enlargement of the spleen while under observation. Blood cultures taken eight hours after the first dose of penicillin and many later ones were all negative. He developed marked congestive failure and severe cerebral symptoms on the second day of penicillin therapy after showing considerable improvement. Thereafter his condition grew steadily worse, and he died of a cerebral embolus on the fifteenth day of treatment after receiving 4,500,000 units of penicillin. At autopsy there were the remains of a vegetative endocarditis of the mitral valve with erosion of most of the chordae tendineae, the stubs of which were hanging loosely. The lower third of the spleen was completely infarcted and necrotic, and there were other infarcts in the rest of the spleen and in the kidneys. Cultures of the heart blood showed no growth, but *Str. viridans* was grown from the vegetation and from the necrotic material in the spleen. The sensitivity of these organisms to penicillin was the same as that of the original blood-culture strain.

Endocarditis with negative cultures. An additional case that was probably one of subacute bacterial endocarditis, in which severe embolic phenomena occurred but all the blood cultures were negative, was also treated with penicillin, with seemingly good results. The patient was a woman of thirty-eight who had severe rheumatic heart disease with mitral and aortic valvular disease but no congestive failure. She had persistent fever and some emboli before treatment, and after one of them she became comatose and developed a hemiplegia. In spite of repeatedly negative blood cultures, the patient was treated with penicillin—20,000 units intramuscularly every two hours for two weeks. She showed rapid and marked improvement, became afebrile and regained all functions, but has had repeated epileptiform seizures, probably the result of cerebral damage from the previous embolism. The patient had a splenic infarct during the third week after treatment ended but for three months has had no evidence of active infection.

TABLE 6. *Autopsy Findings.*

CASE NO.	RELEVANT FINDINGS	BACTERIOLOGY
8	Small, healing vegetations on aortic valve; large splenic abscess; brain and meninges normal.	Cardiac blood and vegetations,* no growth; splenic abscess; *Str. viridans*.
9	Large vegetations on aortic valve.	Cardiac blood, vegetations and spleen, *Str. viridans*.
12	Remnants of vegetations on aortic valve (ruptured cusp); healing leptomeningitis.	Cardiac blood, vegetations and meninges, no growth.
14	Vegetations on aortic and tricuspid valves; purulent leptomeningitis.	Spinal fluid, vegetations and lungs, *Str. haemolyticus* (Group A).
15	Vegetations on aortic and mitral valves; ruptured aortic cusp.	Cardiac blood, no growth; vegetations, gonococci.
16	Vegetations on mitral valve; leptomeninges appeared normal.	Cardiac blood and meninges, no growth; vegetations, nonhemolytic coagulase-negative *Staph. aureus*.

*A few organisms were seen in direct smears.

CASES OF ACUTE BACTERIAL ENDOCARDITIS

A few apparent cures in cases of acute bacterial endocarditis treated with penicillin have been reported, but in most cases the treatment was unsuccessful.[13–16, 23–26] The diagnosis is difficult to make with certainty during life. It is strongly suspected, however, in cases in which there is persistent bacteremia without an obvious focus or after apparent improvement following a bacterial infection, when there are embolic phenomena and when cardiac murmurs appear for the first time and persist or change rapidly in character under observation. Brief résumés of 4 proved and 3 suspected cases are presented here. The significant data are shown in Tables 1 through 6. The cases will be considered, for convenience, according to their bacterial etiology.

Pneumococcal endocarditis. There were 2 cases in which pneumococcal bacteremia persisted following pneumonia in spite of sulfonamide therapy. In these cases the possibility of pulmonary thrombophlebitis must be considered in the differential diagnosis. The first of these (Case 10, Fig. 10) was that of a thirty-five-year-old man who had rheumatic heart disease with mitral insufficiency and was apparently well compensated. He had persistent Type 7 pneumococcus bacteremia following temporary improvement under sulfadiazine and then developed petechiae in the conjunctivas and

enlargement of the spleen. He was treated with heparin intravenously and with 15,000 units of penicillin intramuscularly every two hours. Blood cultures taken four hours after the first dose and

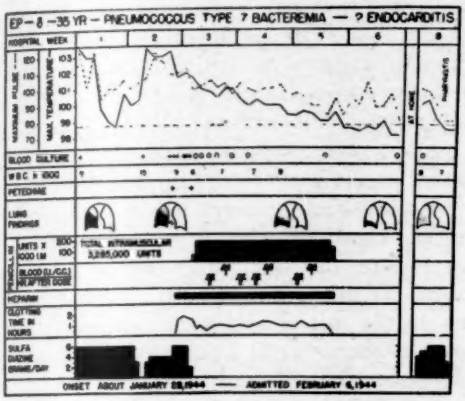

FIGURE 10. *Case 10.*

This patient had rheumatic heart disease with mitral insufficiency but was well compensated. Following typical lobar pneumonia he had a persistent bacteremia in spite of sulfadiazine therapy and then developed enlargement of the spleen. A few petechiae appeared before and soon after treatment with heparin and penicillin was started, but he improved rapidly thereafter. He was readmitted and treated with sulfadiazine for an attack of pharyngitis and has been well since then.

many taken later showed no growth. The lungs cleared rapidly. The spleen has receded and is no longer palpable, the heart has remained fully compensated, and the patient has remained well and able to carry on his usual work.

The second patient (Case 11, Fig. 11) had Type 5 pneumococcus pneumonia with bacteremia. This

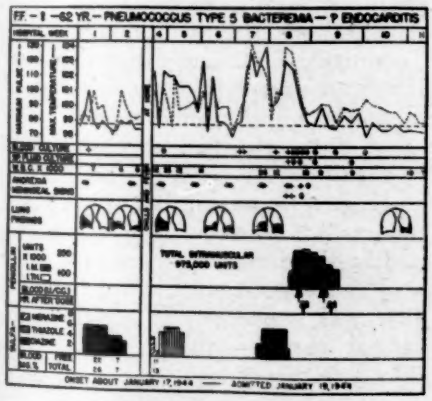

FIGURE 11. *Case 11.*

The patient was originally admitted to the hospital for lobar pneumonia with bacteremia, which apparently responded favorably to sulfonamide therapy. Soon after discharge he had chills and fever and was readmitted. Signs of pneumonia were still present, and the patient did not improve with further sulfonamide therapy. Bacteremia then recurred and persisted in spite of chemotherapy, and he developed purulent pneumococcal meningitis. Treatment with penicillin was followed by complete clinical and bacteriologic recovery.

apparently responded to treatment with sulfadiazine, and he was discharged after two weeks. He returned ten days later with fever, sweats, leukocytosis and persistent signs in the lungs and was again treated with sulfonamides. Bacteremia nevertheless recurred, and the patient developed purulent meningitis with Type 5 pneumococci in the spinal fluid while still on full doses of sulfadiazine. He was then given 15,000 units of penicillin intramuscularly every two hours for six days and also intrathecal injections of 10,000 units after each lumbar puncture. The bacteremia and meningitis cleared rapidly, and the patient has remained well. In this case there were no signs or symptoms pointing directly to cardiac involvement.

In Case 12 (Fig. 12), there was a persistent Type 6 pneumococcus bacteremia without any known focus or antecedent infection. The patient denied any history of rheumatic infections but had an aortic stenosis and regurgitation and was in cardiac failure. Treatment with heparin intravenously and penicillin intramuscularly was begun on what was apparently the eleventh day after the onset of

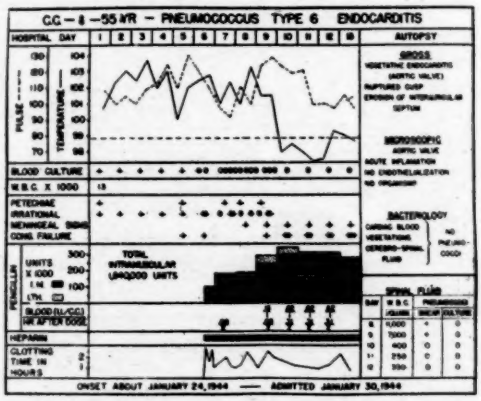

FIGURE 12. *Case 12.*

In this case there was persistent bacteremia with aortic endocarditis and no other demonstrable focus of infection when treatment with penicillin and heparin was started. The patient became comatose, and purulent meningitis was found on the third day of treatment; the latter improved with intrathecal penicillin. Congestive failure was present before treatment, but this increased suddenly and changes in the cardiac murmurs were heard shortly before death.

symptoms. The patient was given 15,000 units of penicillin every two hours for three days and then 25,000 units every two hours. Blood cultures taken eight hours after the first dose and several times thereafter showed no growth. On the fourth day of treatment the patient developed signs of meningitis. A lumbar puncture yielded cloudy fluid with a polymorphonuclear pleocytosis and with gram-positive diplococci in moderate numbers in the smears. Cultures of the first and subsequent cerebrospinal fluid specimens yielded no growth. Penicillin was given intrathecally after each of the lumbar punctures, which were done at twelve to eighteen-hour intervals. On the seventh day, after he seemed to be improving, the patient suddenly developed extreme dyspnea, followed by Cheyne–

Stokes respirations. At that time new and louder to-and-fro murmurs were heard, and the patient died a few hours later. At autopsy there were remnants of an acute vegetative endocarditis of the aortic valve, with rupture of one of the cusps where the vegetations had eroded the endocardium before they broke off. There was no gross evidence of meningitis. Cultures of the vegetations, cardiac blood and meninges showed no growth.

Hemolytic streptococcus endocarditis. Two patients with beta-hemolytic streptococcus endocarditis were treated with penicillin. One of them (Case 14) died after only two intramuscular injections. Cultures of the blood taken before treatment as well as those of the cardiac blood and vegetations at autopsy yielded a Group A streptococcus that did not react with available typing serums.

The other patient (Case 13, Fig. 13) was found to have a Group A, Type 28, hemolytic streptococcus bacteremia three weeks after what was probably

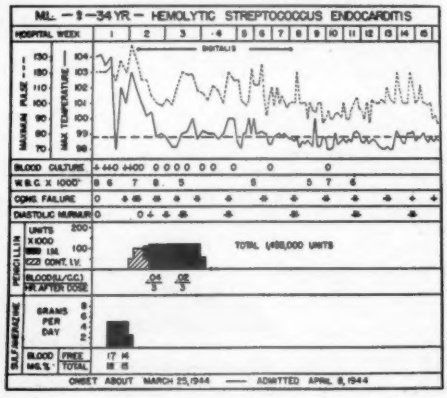

FIGURE 13. *Case 13.*

Persistent bacteremia followed what was probably a septic abortion and persisted during a short course of sulfamerazine. The patient developed congestive failure, which increased soon after penicillin treatment was started, and later a diastolic murmur appeared and persisted. The patient is now fully compensated and does not require digitalis.

a septic abortion. The bacteremia persisted under treatment with full doses of sulfamerazine. The patient had no known antecedent heart disease, but she developed congestive failure before penicillin was started, and this became steadily worse during three days of treatment given by constant intravenous infusion. Treatment was therefore changed to intramuscular injections, 15,000 units every three hours being sufficient to maintain bacteriostatic levels for the patient's organism. Blood cultures taken twenty-four hours after penicillin treatment was begun and all subsequent ones showed no growth. A loud aortic diastolic murmur was heard for the first time on the fifth day of penicillin treatment and persisted thereafter. The patient improved steadily, however, and the heart has gradually become fully compensated so that she is now able to carry on her usual activities without digitalis.

Gonococcal endocarditis. One patient (Case 15) was treated briefly and without success. She was a twenty-year-old woman in the sixth month of pregnancy who had an acute gonorrheal infection treated with sulfonamides five months before admission to the hospital. For four weeks she had had symptoms of a systemic infection. She developed petechiae, joint involvement and positive blood cultures for gonococcus and was then treated with sulfamerazine. Subsequent blood cultures were negative but fever persisted, and after two days of sulfonamides she was started on penicillin — 15,000 units intramuscularly every three hours. Shortly thereafter, however, she developed marked congestive failure and died after only three days on penicillin therapy. At autopsy there were vegetations on the mitral and aortic valves and one of the cusps of the latter had ruptured. Cultures of the cardiac blood yielded no growth, but gonococci were obtained from cultures of the vegetations.

Staphylococcal endocarditis. A fifty-two-year-old man (Case 16) was admitted to the hospital on the third day of an acute febrile illness during which he developed signs and symptoms of meningitis. At the time of entry he also had a generalized petechial and purpuric rash resembling that of meningococcemia, but these lesions later became pustular. A single dose of 5 gm. of sodium sulfadiazine was given on entry, and he was then treated with penicillin intramuscularly in the doses shown in Table 3. He was also given intrathecal injections of 15,000 units of penicillin twice the first day and then once daily for a total of nine injections. Spinal-fluid cultures were sterile on the third day, and blood cultures were negative on the fifth day. The symptoms of meningitis cleared slowly, and the patient became rational on the fifth day. He then developed gradually increasing congestive heart failure, which did not respond to the usual therapeutic measures, and a mitral systolic murmur was heard for the first time. He died after sixteen days of penicillin therapy. At autopsy the meninges appeared to be grossly normal, but there was a vegetative endocarditis of the mitral valve. Cultures of the cardiac blood and meninges gave no growth. Cultures of the vegetations yielded *Staphylococcus aureus* that was nonhemolytic, coagulase-negative and somewhat more sensitive to penicillin than the original blood-culture strain.

COMMENT

The results of the observations presented, when viewed in the light of the data already known and many that have not yet been published, indicate that penicillin is by far the most effective agent now available for the treatment of subacute bacterial endocarditis and for endocarditis caused by other susceptible organisms. It has rendered the blood stream free of bacteria in almost all such cases in which it has been given in adequate doses for at

least a few days. In most cases in which the treatment was carried out for a long enough period, it has not been possible to culture the bacteria from the blood for variable periods after the treatment was discontinued. The proper dosage and duration of treatment have not yet been determined, but the present findings and those of many other writers suggest that in cases of *Str. viridans* endocarditis and probably also in cases due to other organisms it is necessary to give large doses for a fairly long period in order to obtain the most beneficial results.

The bacteria-free and symptom-free interval in each of the surviving cases is shown in Table 1. The results in Cases 6 and 7, in which there seemed to be a favorable response to the recurrent infection, suggest that these patients might have obtained a better result had the first course of treatment been continued with full doses for a longer period. On the other hand, the bacteriologic findings raise the question whether these recurrences represent new infections or relapses of the original infection. In Case 16, the differences in the characteristics of the staphylococcus originally obtained from the blood culture and of the one grown from the vegetation are also of interest in this regard, particularly since the latter was somewhat more susceptible to penicillin than the former and the patient had been treated for sixteen days. The findings in this case likewise suggest the possibility that earlier and more intensive treatment might have been more effective.

The significance of the penicillin concentrations in the blood and their relation to the susceptibility of the organisms are not entirely clear from the limited studies in the present cases. In some cases the clinical response seemed to be accelerated when the dosage was adjusted to maintain continuously a concentration higher than that necessary to inhibit the growth of the patient's organism. In others, however, similar or even better clinical results were apparently obtained in spite of the fact that adequate concentrations were maintained only during part of the interval between injections. The crudeness of the methods used may account in part for these discrepancies. It is interesting to note that while the patients were in congestive failure and on a limited fluid intake, somewhat smaller doses were usually required to maintain adequate blood concentrations.

Many factors probably influence the outlook for successful treatment with penicillin in cases of bacterial endocarditis. The susceptibility of the organism is only one of them. The amount of damage already done to valves and other structures has an important influence. Congestive failure developing or progressing rapidly, either before or during the course of treatment, is another significant factor. Obviously if valve cusps, chordae tendineae or septal structures have already been eroded, the elimination of further infection will not necessarily result in any functional repair. The amount of damage already sustained by other vital organs is also a factor. All these points demonstrate the need for early diagnosis and early intensive treatment. Because of the more rapid course in cases of acute bacterial endocarditis, once this condition is established, it is particularly important to treat all patients who have persistent bacteremia as though they had potential cases of endocarditis.

Careful management of convalescence in so-called "arrested" or "cured" cases of subacute bacterial endocarditis is also necessary, and this is probably equally true in cases of endocarditis due to other bacteria. Embolic phenomena may occur for some time after the blood becomes bacteria-free. Each such occurrence carries with it the threat of further damage to valves or other underlying structures in the heart from which the emboli are released, as well as possible injuries where they become lodged. Severe cardiac failure may follow these occurrences. Reasonable treatment should therefore include a regime similar to that used in the care of cases of acute coronary thrombosis. This regime comprises an adequate period of inactivity to permit repair, followed by a very gradual increase in activity well within the limits of the cardiac reserve. The length of the convalescent period depends on an estimation of the cardiac status before and after treatment, the return of the white-cell count and sedimentation rate to normal and the possible occurrence of complications and embolic phenomena.

Infected foci in abscessed teeth, diseased tonsils and so forth should be eliminated. It is suggested that a course of treatment with penicillin or sulfonamides or both be begun just before tonsillectomy or tooth extractions and continued for a brief period thereafter, it being assumed that the original site remains vulnerable to reinfection with bacteria that may be released at the time. The finding at autopsy of infected abscesses at the site of splenic infarcts further suggests that a similar course of therapy would be advantageous immediately after any embolic manifestations in spite of the finding of negative blood cultures at such times. There may still be viable organisms in the embolus and at the site from which it was released.

Details of the autopsy findings are to be reported separately. Evidence of some healing was found in every case in which penicillin was given for a few days. In these cases, however, the amount of damage in the heart was usually sufficient to account for the cardiac failure.

Heparin was used in 5 cases of the present series. At first it was thought that the heparin was responsible for the occurrence of petechiae and emboli soon after the treatment was begun. The possible value of effectively eliminating the vegetation at the time when the antibacterial therapy was being carried out was considered as an advantage of the heparin. Subsequent observations in other cases of this series

and those made by other workers have shown a similar course under treatment with penicillin alone. No advantage has therefore been found to justify the additional effort and risks of heparin treatment. A true evaluation of the relative merits of the combined treatment is extremely difficult and requires a considerably greater experience than is represented in the present series.

Summary and Conclusions

The relevant data are presented in 9 cases of subacute bacterial endocarditis that were treated with sodium penicillin at the Boston City Hospital during 1944. The dose generally used was 25,000 units intramuscularly every two hours for two weeks. Seven of the patients are alive and have been free of evidences of active infection for one to eleven months.

Two patients had recurrence of infection, one after four months and the other after only one month. It is not certain whether these recurrences represent reactivation of the original infection or reinfection.

An additional fatal case of *Streptococcus viridans* endocarditis was treated. Another extremely severe case with a characteristic clinical course of subacute bacterial endocarditis with multiple emboli improved, and the patient was living three months after treatment, but no bacteria could be grown from the blood before penicillin was started.

All the fatal cases had severe heart failure resulting from extensive damage to cardiac structures.

The findings in 7 cases of acute bacterial endocarditis treated during the same period are also presented. Small doses were generally used in these cases because of the greater susceptibility of the organisms. In 3 of these cases, — one caused by a Type 7 pneumococcus, the second by a Type 5 pneumococcus and the third by a Group A, Type 28, hemolytic streptococcus, — the patients are living and well. The diagnosis in all the fatal cases was confirmed at autopsy but in those who survived is only highly probable.

Heparin was used together with penicillin in 3 of the *Str. viridans* cases and in 2 of those due to pneumococcus. There appeared to be no benefit from this therapy to justify the additional effort and risk.

The present findings suggest that early and intensive treatment with penicillin maintained for an adequate period offers the best hope for recovery or arrest of infection in cases of subacute and acute bacterial endocarditis. The optimum dosage and duration of treatment are yet to be determined.

The importance of early diagnosis and treatment, as well as the careful and intelligent management of the convalescent phase, are stressed.

We are indebted to the members of the visiting and resident staff of the hospital, who co-operated generously in the study of these cases. The routine bacteriologic studies were done by Miss Marion E. Lamb and her associates at the Mallory Institute of Pathology.

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CLINICAL NOTE

A NEW POCKET PRISMATIC MICROSCOPE

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A NEW compact microscope is shown in Figure 1. This pocket microscope weighs 1 pound and 6 ounces, and measures 4½ inches in length, 2½ inches in width and 5¼ inches in height. Conventional eyepieces and objectives (low-dry, high-dry and oil immersion) are used, giving a magnification and size of field comparable to the ordinary laboratory microscope. The action of a large microscope is made possible in this diminutive model by bending the light rays through four right-angle prisms in line. A focal length of 175 mm. is maintained, and this allows the use of regular objectives and eyepieces. There is no appreciable loss of magnification or clarity.

This workshop model possesses only a coarse focal adjustment, but a fine adjustment can be added to the precision-built, factory instrument. There is some inevitable reflectionary loss of light as the rays pass through the prisms, but a similar loss of light occurs in the large binocular microscopes. The substage condensing of light, normally done with an Abbé condensing lens, has been practically accomplished by using a mirror of short focal length (5-cm. radius and +10,−10 curve) that reflects a completely satisfactory cone of light on the slide. The occasional desire for the reduction of light

FIGURE 1.

usually accomplished with a diaphragm is performed by a mirror adjustment by means of a small knoblike button at the side of the base.

This prismatic microscope is presented as a small, light, powerful instrument for bedside use.

78 Washington Avenue

MEDICAL PROGRESS

THE CLINICAL IMPORTANCE OF THE RH BLOOD TYPE (Concluded)*

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RH INCOMPATIBILITY IN PREGNANCY

In contrast to the type of mild or only moderate transfusion reactions described above in men and in nongravid women, it has been recognized for several years that during pregnancy, or shortly thereafter, women may have severe transfusion reactions when given presumably compatible blood during a first transfusion. In 1939, Levine and Stetson[40] reported a case of intragroup agglutination in a pregnant woman in which they demonstrated an abnormal agglutinin; they suggested that this had resulted from sensitization of the mother to some agent present in the fetus, inherited from the father. They did not give this antigen a name, and only later recognized it as similar to the Rh factor described by Landsteiner and Wiener.

A typical instance of this sort is illustrated in the following case.

CASE 4. *Hemolytic reaction to first transfusion of Rh+ blood.* A 26-year-old woman at term in her third pregnancy gave the following history. The first pregnancy had resulted in a normal child, and the second, in an infant with moderate jaundice shortly after birth and anemia lasting 6 weeks. Recovery occurred without transfusion. Shortly before admission, fetal activity ceased, and a few hours later a stillborn infant was delivered. At necropsy the diagnosis of erythroblastosis fetalis was substantiated.

There was considerable post-partum bleeding; this was uncontrolled by vaginal packing so that transfusion was necessary. The husband, being Group 0 and apparently compatible, was used. After 300 cc. of blood had been infused the patient showed signs of shock and passed a small amount of bloody urine. Thereafter her condition was precarious, with the development of anuria and jaundice. No further transfusions were given, and the patient recovered in about 3 weeks. Impaired renal function persisted, however.

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Blood typing revealed that the patient was Group 0, Rh−; her husband, Group 0, Rh+; and the two living children, Group 0, Rh+. The patient's serum showed a large amount of anti-Rh agglutinin.

In contrast to the forewarning that usually occurs in transfusion reactions due to Rh incompatibility in men or in nongravid women, in whom the first transfusion is uneventful and only the second may produce signs of a hemolytic reaction, in pregnancy the first transfusion given to the Rh— woman who has had an infant with jaundice, anemia or other signs of hemolytic anemia or erythroblastosis fetalis may result in a serious if not fatal reaction. In such cases it is found that the husband and the child are Rh+, that the mother is Rh— and that her serum contains anti-Rh agglutinins. As has been pointed out by Levine, a modified compatibility test will occasionally give warning of such an incompatible transfusion, in that the donor's cells may be agglutinated by the recipient's serum after incubation for half an hour at 37°C. This test when negative, however, cannot be relied on as evidence of no danger of a transfusion reaction, since, as has been pointed out, the test-tube agglutination method fails in more than 50 per cent of the persons in whom such antibodies are present.

A carefully taken history of the previous pregnancies, with the result of each, may occasionally forewarn of the danger of an intragroup transfusion reaction in women who have borne one or more children. In such cases a story of jaundice or anemia in a child or of a late stillbirth should always be regarded as significant, and the danger of a transfusion reaction should be avoided by careful grouping, Rh typing and cross-matching.

In contrast to the statistics for hemolytic transfusion reactions in men and nongravid women, severe reactions due to Rh incompatibility occur when immunization is the result of pregnancy. Thus, in 32 cases, 21 patients had moderately severe reactions and 6 had severe reactions, 5 of the latter dying. Such evidence alone is sufficient proof of the danger of transfusion in obstetric patients who are Rh—.

Another and even more serious type of reaction in pregnancy is illustrated below.

Case 5. *Hemolytic reaction to second transfusion of Rh+ blood.* A 36-year-old patient had had four pregnancies, the first three children being alive and well and the fourth having died of prematurity and pulmonary atelectasis after 7 months of gestation. The fifth pregnancy was terminated by cesarean section at 7 months on account of a complete placenta previa, and the infant succumbed to atelectasis. The mother required a transfusion, the blood being obtained from the husband, a presumably compatible donor, later proved to be Rh+; no reaction followed. A sixth pregnancy four years later resulted in the precipitate delivery at 8 months of an infant with erythroblastosis fetalis, who died in 12 hours. The placenta was large, and there was considerable hydramnios.

Immediately after delivery continued bleeding from a hole in the uterus necessitated hysterectomy. Because of a hemorrhage, 500 cc. of presumably compatible blood (Donor 1) was given while the patient was still anesthetized. This was followed by a hematemesis and symptoms of shock. In the following 3 hours three more transfusions (Donors 2, 3 and 4) were administered, with increasing shock, anuria and jaundice. Finally, transfusions from Donors 5, 6 and 7, especially chosen for their Rh type, were given with no untoward reaction. Anuria continued, however, and the patient became uremic and died in about 2 weeks.

Blood typing proved the patient was Group 0, Rh−; the husband, Group 0, Rh+, the children, Group 0, Rh+, Donors 1, 2, 3 and 4, Group 0, Rh+; and Donors 5, 6 and 7, Group 0, Rh−. The patient's serum contained a high titer of anti-Rh agglutinins when tested after the later transfusions. This Rh− woman, married to an Rh+ man, had three normal Rh+ infants. No sensitization occurred due to these pregnancies, as proved by the necropsy examination of the fourth and fifth infants and the uneventful transfusion of Rh+ blood following the fifth pregnancy. This transfusion, however, produced sensitization to the Rh factor, with the development of agglutinins. The sixth pregnancy probably increased the sensitization. The fetus was severely damaged by the agglutinins present in the mother's circulation and died of erythroblastosis. The several transfusions that were required produced serious hemolytic reactions, even though they were from homologous donors. Later typing proved that the reactions were due to the interaction of the infused Rh+ cells with the high-titered anti-Rh agglutinins in the patient's serum. Despite three compatible transfusions of Rh− blood, taken without reaction, the patient succumbed. Thus, although the pregnancies had produced no sensitization, a single transfusion of Rh+ blood sensitized the patient, with resulting harm to the next Rh+ fetus and to herself after transfusion of Rh+ blood.

Since some of the earliest symptoms of incompatible blood transfusion are subjective, it is generally advisable to avoid the use of whole blood in anesthetized patients.

In Rh— women sensitized by previous transfusion and in whom this sensitivity has been increased by pregnancy with an Rh+ fetus, transfusion reactions are almost invariably fatal, with, in addition, erythroblastosis producing death of the fetus before term. This was true in all 3 such cases in our series.

The last important complication of Rh incompatibility in pregnancy is the development of erythroblastosis in the fetus as the result of sensitization of an Rh— woman by transfusion of Rh+ blood. The following case is illustrative.

Case 6. *Erythroblastosis fetalis resulting from incompatible transfusions.* A 23-year-old white woman gave the following history. At the age of 16 she had had a major operation for removal of a tumor and, because of subsequent bleeding, had required six blood transfusions, which were given without reaction. Two years later the recurrence of bleeding following surgery required four further transfusions. These produced no serious reactions, but the patient apparently felt uncomfortable and subsequently failed to show the expected rise in hemoglobin level. One year later, her first pregnancy ended at term in a stillborn infant with the congenital hydrops type of erythroblastosis fetalis.

Blood typing proved the patient to be Group 0, Rh−, and the husband, Group 0, Rh+. Two of the donors previously used were Rh+. The patient's serum contained a high titer of anti-Rh agglutinins. The following year, and again two years later, pregnancies resulted in stillborn infants with severe erythroblastosis of the fetal hydrops type.

This Rh— woman received multiple transfusions, which caused the development of a high titer of anti-Rh agglutinins. Her Rh+ husband transmitted this factor to his offspring. The usual history obtained in women having infants with erythroblastosis states that the first child is unaffected, even

though Rh+, because the pregnancy initiates the stimulation of the mother's antibody production. In this case, previous transfusion caused antibody development, and even the first child suffered from severe erythroblastosis fetalis. Succeeding pregnancies with Rh+ infants resulted in similar catastrophes.

Erythroblastosis fetalis resulting from sensitization produced by the transfusion of an Rh— woman with Rh+ blood is always the worst form of this disease. Thus, in the 25 women in our series, 18 had two or more infants with erythroblastosis fetalis. Of 32 of these fetuses or babies, 28 died in utero, and 4 lived for less than twenty-four hours. Three women each had a single normal infant, and each of the latter was Rh—. In such cases, the sensitization may be established long before pregnancy begins, so that the Rh+ fetus begins to suffer harm early in gestation, probably from about the eighth to tenth week, when its red cells first develop Rh agglutinogens. Such infants are prone to die in utero, usually in the seventh to eighth month of gestation, and even those that are born alive, usually before the end of term, succumb within a day or two. Although this complication of pregnancy may occur relatively infrequently, it represents a major catastrophe in the life of such women and in their child-bearing potentialities. Only women married to heterozygous Rh+ men will succeed in having living children, and these will be Rh—. Since 38 per cent of the population is R+ homozygous, sensitization of the Rh— woman of child-bearing age by transfusion of Rh+ blood remains a serious hazard.

Because of the increasing use of stored blood and the frequency of transfusion as a therapeutic measure, the danger of immunization of women of child-bearing age is an increasing one. A recent development that makes this danger even greater is the use of resuspended red cells from which the plasma has been removed for the production of plasma. Since these cells have been made readily available in many large cities, especially on the public wards of hospitals, transfusion of resuspended cells has been liberally used. Since many women of child-bearing age have been given such blood without preliminary typing of the recipient for the Rh factor, the danger of sensitization with Rh+ cells has increased and the successful termination of future pregnancies has thereby been jeopardized, and needlessly so. Rh typing is therefore an important preliminary to the transfusion of women, particularly those in the child-bearing age.

Erythroblastosis Fetalis

This disease has already been mentioned as a sequel to sensitization of the Rh— mother to Rh+ red cells, with the development in the mother's serum of anti-Rh agglutinins. These can readily pass the placental barrier and affect the Rh+ infant just as soon as a sufficiently high titer has developed in the mother's blood. This important discovery, the outstanding contribution to our understanding of erythroblastosis fetalis, was first made by Levine, Katzin, and Burnham[41] in 1941. It was proved conclusively in numerous subsequent studies by Levine and his co-workers,[42–45] and this has been confirmed by many others.[46–50] The disease usually develops in the second or subsequent Rh+ infant, since it usually requires at least one pregnancy to initiate sensitization of the Rh— mother, when a second or subsequent pregnancy restimulates her to the development of stronger agglutinins. Sometimes the first child to be so affected develops relatively mild symptoms of jaundice and anemia and recovers spontaneously.

The classic symptoms and signs of this disease are jaundice within twenty-four to forty-eight hours and the development of anemia, often at birth but more regularly by the third or fourth day, becoming most profound by the end of the seventh or the eighth day if the disease is not of the fulminating type. Death due to anemia and anoxia, however, may occur within the first twenty-four to forty-eight hours. Splenomegaly and hepatomegaly are quite frequently present. Edema and even universal hydrops may be noted in the most severely affected infants immediately after birth or within the first day. A large number of nucleated erythrocytes often occur in the peripheral blood, but this finding is not necessarily a criterion of the disease. Finally, erythroblastosis may develop in infants who do not have hemolytic anemia due to Rh incompatibility, especially those with infection, with congenital malformations of the heart, with anoxia due to atelectasis of the lungs and with intracranial hemorrhage, and even extremely premature infants. In the usual case, the final laboratory confirmation of the diagnosis is the demonstration of an Rh— mother, an Rh+ father, an Rh+ infant and anti-Rh agglutinins in the mother's serum.

In the severe forms, the jaundice often increases rapidly and is then augmented by an obstructive jaundice, owing to blockage of the bile capillaries in the liver and a disturbance of function of the hepatic cells. This obstruction may be so intense, with all the signs and symptoms so overshadowing the anemia and other signs of erythroblastosis fetalis, that the patient is thought to be suffering from congenital obliteration of the bile ducts. In fact some patients with hemolytic anemia have been subjected to exploratory operation for such a congenital defect before the diagnosis of hemolytic anemia was made.[51, 52] Hemolytic anemia of the newborn tends to become severer in succeeding pregnancies, with greater degrees of jaundice and earlier intrauterine death of the infant, with universal hydrops and anemia.

Treatment of the condition consists chiefly of the early recognition of the disease and the use of trans-

fusions of compatible blood, which for the first ten to fourteen days of life should be Rh—. For this, the mother's washed cells or, still better, whole blood from an Rh— donor may be used.[42, 53–57] The rationale for the use of Rh— blood is that many of these infants still have in their circulation anti-Rh agglutinins that are not combined with their own Rh+ cells and are therefore potentially active against other Rh+ cells infused into the infant's circulation. Rh— cells cannot be affected by such abnormal agglutinins and have been proved to survive in the infant's circulation.[52, 58]

Infants with erythroblastosis should not be permitted to receive the mother's breast milk, since it has been proved that the agglutinins may be present therein and, after absorption through the stomach, may produce further destruction of the Rh+ cells.[50, 59, 60]

One of the complications of erythroblastosis fetalis of the severe icteric type (icterus gravis familiaris) is damage to the nuclei of the brain, a condition known as kernicterus. When this occurs, the infant exhibits convulsions, twitching, opisthotonos and respiratory difficulties. Death may occur in the first week. If the baby survives, he is sometimes left with an impaired nervous system, with spastic paraplegia and mental retardation later in life. Fortunately, this complication of the severely icteric type of erythroblastosis occurs in less than 16 per cent of all such patients. The majority of children who recover develop normally in later life and show no damage from the early hemolytic anemia. One late complication in infants who have been severely jaundiced at birth is a deep-green staining of the deciduous teeth. This is directly related to the degree and the time of the jaundice in intrauterine and neonatal life and is the result of pigment deposition in the growing enamel. It does not affect the permanent teeth and can therefore be ignored.

Testing for Rh Factor and Anti-Rh Agglutinins

There are a few practical considerations regarding laboratory technics involving the Rh factor and anti-Rh agglutinins. In performing tests for the Rh factor, it is important to make certain that the red cells are obtained from freshly drawn blood. The Rh agglutinogen is apparently more fragile than are the A and B agglutinogens and tends to give weaker reactions the longer the red cells remain outside the body, particularly if they are suspended in normal saline solution; thus, false negative tests may result. The details of the technic of Rh testing, including the precautions necessary for accuracy, have been best described by Wiener,[32] by Levine[61] and by Taylor.[62]

The anti-Rh serum used for Rh determinations should be tested frequently against known Rh+ and Rh— cells. Such serum, especially if originally low in potency, tends to deteriorate on standing, even when stored in the refrigerator. In general, the serum should be of the highest possible potency and of wide specificity. At least four types of serum have already been identified, namely, one that agglutinates only 30 per cent of Rh+ cells (anti-Rh″), one that agglutinates 73 per cent of Rh+ cells (anti-Rh′), one that agglutinates 85 per cent of Rh+ cells (anti-Rh_o) and one that agglutinates 87 per cent of Rh+ cells (anti-Rh). For complete differentiation, more than one of the first three serums may be necessary.

It has been advised that the demonstration of anti-Rh agglutinins be carried out in the test tube with a dilute suspension of Rh+ cells from a known donor and freshly drawn serum from the subject under investigation.[32, 53, 61–65] This test, however, is not always conclusive, since a new type of antibody, the so-called "blocking antibody" of Wiener,[66] the "incomplete antibody" of Race[67] or the "inhibitor substance,"[68] is present in more than 50 per cent of the serums of women who have been sensitized by transfusion or pregnancy, or both; this inhibits agglutination of a dilute suspension of Rh+ cells by anti-Rh agglutinin in a test tube on incubation at 37°C. Wiener has suggested a test for this blocking antibody. Furthermore, a rapid method for the demonstration of anti-Rh agglutinins that avoids difficulties resulting from the inhibitor substance has been described.[69] It must therefore be recognized that anti-Rh agglutinins may exist in the serum of sensitized persons without necessarily being demonstrable by the test-tube incubation method of detection and that the so-called "modified compatibility test" cannot be used as the sole safeguard in cross-matching preliminary to transfusion.

Practical Applications

That the determination of the Rh factor has practical value has been briefly presented in the preceding pages. More comprehensive reviews have been written by Potter,[70] by Davidsohn[71] and by Boyd.[72] From the accumulated facts, certain conclusions are permissible.

It is of increasing importance that recipients of transfusions, especially of multiple transfusions, be typed for the Rh factor. The Rh— individuals (13 per cent of the white population) who receive Rh+ blood may develop anti-Rh agglutinins, which will interfere in succeeding transfusions with complete benefit from the infused blood. Transfusion reactions of increasing severity will then occur, and in some cases these may cause serious kidney damage, although death does not commonly occur as a result of Rh sensitization from transfusion alone. An attempt to evaluate the frequency with which men or nongravid women can develop anti-Rh agglutinins when given Rh+ cells was made by repeatedly injecting small amounts of such cells into Rh— subjects. Six of 10 men developed a

satisfactory titer of agglutinins, but 4 developed none at all and showed no reaction at the end of a series of injections when given a larger amount of Rh+ blood. It remains for statistical studies, particularly those on men in the armed forces, where large amounts of whole blood have been given, to determine how many persons can develop anti-Rh agglutinins as the result of stimulation by transfusion alone. With the increasing therapeutic use of whole blood and its greater availability in blood banks, the Rh factor has become increasingly important.

Regarding pregnancy, it must first be realized that not every Rh— woman married to an Rh+ man will suffer harm from pregnancy with Rh+ infants. Owing to the occasional newspaper report of the birth of infants with erythroblastosis fetalis and the peculiarities of the mother's blood that produced such disturbances, flurries of excitement have occurred, and many women have been forewarned that, because they have Rh— blood, their pregnancies are sure to suffer forever after. Statistically the marriage of an Rh— woman to an Rh+ man occurs in 12 per cent of all marriages. Erythroblastosis fetalis has been stated to occur about once in two hundred deliveries (Javert[73] and Schwartz and Levine[74]), but was found as frequently as once in about one hundred and fifty deliveries in our series. Therefore, only one in about fifteen marriages between an Rh— woman and an Rh+ man will lead to erythroblastosis fetalis in the offspring, and this usually does not occur until the second or later pregnancy. In addition, the factors in isoimmunization by pregnancy alone can be resolved further on the basis of whether the father of the child is homozygous, that is, the offspring of two Rh+ parents, and carrying two Rh+ genes, or heterozygous and carrying only one Rh+ gene in his cells. This is not always detectable by Rh testing of his cells but is of practical importance. In the former case, all the children must be Rh+, although heterozygous; in the latter case, half the children will be Rh— and will thus escape harm by the agglutinins of the mother if such have developed through previous transfusion or pregnancy. In addition, to produce erythroblastosis fetalis, it is assumed that the placental barrier must be faulty and that the fetal Rh+ cells must be able to enter the maternal circulation.

Since the placental barrier is assumed to hold back cellular elements, since some persons do not respond to Rh antigen by anti-Rh production, since 49 per cent of Rh+ men are heterozygous and can father Rh— children and since two or more pregnancies are usually necessary to produce infants suffering from erythroblastosis fetalis, this disease remains a fairly rare complication of Rh differences between mates. It may even be suggested that other incompatibilities between man and wife are more hazardous to married life than differences in the Rh factor.

In attempting a prognosis for further pregnancies in any given family, it is of value not only to test the mother's blood for anti-Rh agglutinins in the second and subsequent pregnancies, but also to try to determine whether the father is homozygous or heterozygous. Should he be homozygous and one infant with erythroblastosis has been born, all subsequent infants will be similarly affected and further pregnancies may be contraindicated.

An additional laboratory measurement of prognostic value is the determination of the increase in anti-Rh titer during pregnancy in women who have had a previous infant with erythroblastosis fetalis or who have been sensitized by an Rh+ transfusion. In such cases, the agglutinin titer tends to increase relatively late in pregnancy, usually by the seventh or eighth month. Earlier in pregnancy, the presence of anti-Rh agglutinins has not been proved harmful to the fetus, since even a high titer of antibodies does not usually cause abortion at the second or third month of gestation. Possibly this is related to the relatively late appearance in the fetus of red cells carrying the Rh agglutinogen. They have been found by us in a three-month fetus on four separate occasions, by Stratton[75] in a 48-mm. embryo and by Bornstein and Israel[76] in a 17-cm. fetus.

If the titer does suddenly rise, the delivery of an infant who seems large enough to be viable at about eight to eight and a half months of gestation results in a milder degree of erythroblastosis than if the infant had been permitted to remain in utero and thus subjected to a high titer of agglutinins until term. The following case is illustrative.

Case 7. *Increase in anti-Rh titer during pregnancy.* A 30-year-old woman had had a normal first-born child and a second child who died of erythroblastosis on the 3rd day of life. The husband proved to be Rh+; the wife, Rh−; and the two children, Rh+.

During the third gestation, tests on the mother's serum for anti-Rh agglutinins were as follows: at 6 months, negative; at 7 months, negative; at 7½ months, low agglutinin titer; at 8 months, moderate agglutinin titer; and at 8½ months, high agglutinin titer. Because of the sudden increase in antibodies against the Rh factor late in pregnancy, delivery was induced at 8½ months, and a 5-pound, Rh+ infant was obtained. Within 24 hours, jaundice and anemia were noted, but after three transfusions the infant recovered and remained well.

In this case, although a second child had died at term of erythroblastosis, a third pregnancy resulted in a child surviving after several transfusions.

This is one of the two methods of proved value in assisting the previously sensitized Rh— mother to have a living Rh+ infant. In 41 cases of early induction of delivery on account of a rising titer of anti-Rh agglutinin, there have been 32 living and 9 dead children. The other method, particularly applicable in the mating of a homozygous Rh+ man to a sensitized Rh— woman, is artificial insemination using an Rh— donor. This has been uniformly successful in 6 cases. Potter and Willson[77] have recently reported a similar experience. The

emotional adjustments necessary for this form of treatment do not recommend it for widespread use.

Conclusions

The Rh blood type, present in about 87 per cent of the white population, is of practical importance almost exclusively to the persons who lack it. In the latter, repeated transfusion of Rh+ blood cells may lead to increasing hemolytic reactions, owing to the interaction of anti-Rh agglutinins initiated by the first Rh+ transfusion with the specific agglutinogen of the infused cells.

Rh— women married to Rh+ men may be sensitized by means of one or more pregnancies involving an Rh+ fetus, the Rh factor being inherited as a dominant trait. Although this only occurs in one of about fifteen such matings, once so immunized, the woman cannot safely be given even one transfusion of untyped or Rh+ blood, since it may produce a serious, even fatal, hemolytic reaction.

A single Rh+ transfusion to an Rh— woman, married to an Rh+ man, may initiate the antibody response, and a subsequent pregnancy with an Rh+ fetus may end in the severest form of erythroblastosis fetalis in the infant. Women of child-bearing age must therefore be protected against this potential danger.

Infants who have erythroblastosis fetalis should be treated early and actively with transfusions of Rh— blood. The diagnosis of the usual type of erythroblastosis fetalis is dependent not only on the well-known physical signs but also on the laboratory demonstration of anti-Rh agglutinins in the Rh— mother of an Rh+ infant of an Rh+ father.

The laboratory technics for testing for the Rh factor and anti-Rh agglutinins require certain safeguards and experience.

Finally, Rh typing is necessary for all recipients (male or female) of repeated transfusions, for all women requiring transfusion, to avoid serious reactions in those who have borne an erythroblastotic infant and to avoid sensitization of Rh— women of child-bearing age, for the listing of Rh— donors for emergency use and for the procurement of Rh— banked blood to be given to Rh— patients.

An anti-Rh determination is particularly indicated in pregnant women whose histories show that one or more previous pregnancies ended in late stillbirths, infants with severe jaundice or anemia or even infant deaths apparently due to hemorrhage or anoxia, in Rh— women who have received transfusions, especially from their husbands and in Rh— women married to Rh+ men who have had one or two children and may therefore have been sensitized to the Rh factor.

Some practical benefit may be derived from following the anti-Rh agglutinin titer of the serum during the pregnancy of the woman who has had a previous child with erythroblastosis fetalis.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31171

PRESENTATION OF CASE

A fifty-two-year-old man was admitted to the hospital because of difficulty in swallowing.

Six weeks before admission, the patient noticed difficulty in swallowing solids for the first time. He had to follow solid food with large amounts of tea and other liquids, otherwise hiccoughs and slight substernal pain ensued. This difficulty progressed, and an uncomfortable "stretching sensation" with each swallow became pronounced about the area of the midsternum. Over a period of four weeks the dysphagia became so marked that he could swallow only liquids and mushy foods. He had no nausea or regurgitation and had lost little or no weight. He felt well and did not become fatigued easily. A barium swallow and chest x-ray in the Out Patient Department two weeks before admission showed the swallowing function to be normal. The esophagus was rather irregularly dilated to a point about 16 cm. above the esophagogastric junction, where there was a constant narrowing with probable shelf formation extending for a distance of 7 cm. There was no ballooning in this area, and the barium passed through rather rapidly without evidence of obstruction. The mucosal pattern did not appear to be normal in this area, and there was probably a small amount of destruction. The remaining 9 cm. of esophagus appeared to be normal. Two weeks before admission the patient allegedly had one tarry stool. He had had frequent nosebleeds in the past few weeks and thought that he had regurgitated small amounts of blood. The patient believed that he had become quite pale in the past two years.

At twenty-two years he had had pneumonia, and in his early twenties gonorrhea. At twenty-five years of age he had suffered from migratory joint pains, was told that he had rheumatism and remained in the hospital for two months. The following year he had a tonsillectomy. He was seen frequently in the Out Patient Department at the age of forty-eight, four years before admission, because of severe substernal pain on exertion, which was promptly relieved by rest or nitroglycerin. X-ray films at that time showed the heart to be enlarged across the base, with a prominent left auricle and pulmonary conus. The lung fields and diaphragm were normal. An electrocardiogram was thought to be within normal limits. The blood pressure was 120 systolic, 80 diastolic. The anginal pain improved, but he continued to be moderately dyspneic on exertion.

Physical examination revealed a slightly obese, well-developed man in no distress. The chest was moderately emphysematous, and a few inspiratory rales were heard at the apices. The apex beat was 1 cm. to the left of the midclavicular line. A loud first sound was heard at the apex. There was a questionable early diastolic murmur along the left sternal border in the third interspace. The aortic second sound was greater than the pulmonic. The abdomen was normal. There was no lymphadenopathy. A rectal examination revealed an enlarged, firm, smooth prostate.

The temperature and respirations were normal. The pulse was 75.

Examination of the blood showed a red-cell count of 5,160,000 and a white-cell count of 9200. Examination of the urine was negative. Stools were guaiac negative. The prothrombin time was 23 seconds (normal, 18 to 20 seconds). The serum nonprotein nitrogen, the protein and the chloride values were normal. An electrocardiogram showed normal rhythm at 85, a PR interval of 0.18 second, normal axis, small Q_3, upright T_1, T_2 and T_4 and flat T_3.

X-ray films of the chest showed no evidence of metastatic cancer. There appeared to be some enlargement of the left auricle and perhaps of the left ventricle.

On the sixth hospital day the patient was esophagoscoped. The instrument passed readily to approximately 29 cm. below the teeth, where there was marked narrowing of the lumen to a diameter of approximately 3 mm. There were reddening, slight irregularity and erosion of the anterior wall. Seven hours after esophagoscopy the patient became slightly dizzy and cyanotic, with mild, nonradiating, substernal pain. The blood pressure was 60 systolic, 40 diastolic. The temperature was 100.6°F., and the pulse was irregular and thready, with a rate of about 110. The patient perspired profusely, became unresponsive and developed convulsive twitchings. A few seconds after oxygen was administered he regained consciousness. An electrocardiogram revealed auricular fibrillation, with a rate of 155, normal axis, low upright T_1 and upright T waves in Leads 2, 3, CF_3, CF_4 and CF_5. There were two ventricular premature beats in Lead 1. In some areas the P waves seemed prominent and suggested runs of paroxysmal auricular tachycardia. A repeat electrocardiogram three hours later was unchanged, except that the rate had increased to 175. Two hours after 6 cc. of Cedilanid had been given, the patient

*On leave of absence.

was comfortable and oriented, with a strong, regular pulse, at a rate of 90, and a blood pressure of 105 systolic, 65 diastolic.

On the following day he passed about 300 cc. of dark blood by rectum. He became pale, and the red-cell count dropped to 3,300,000, and the blood pressure to 90 systolic, 60 diastolic, with a pulse of 90. He had mild substernal pain and coughed up a small amount of blood. He developed purpuric spots over his arms and legs (similar spots had allegedly been appearing and disappearing during the previous month).

X-ray films of the chest showed clear lung fields, with no air in the mediastinum. A repeat film on the eighth hospital day showed linear areas of increased density opposite the fourth rib anteriorly that were not present previously. Two subsequent films showed no change. On the eleventh hospital day the stools were tarry. The red-cell count had dropped to 2,600,000. A repeat prothrombin time was 23 seconds (normal, 18 to 20 seconds). A blood smear showed 84 per cent neutrophils, 10 per cent lymphocytes and 4 per cent monocytes, with almost no platelets and no abnormal red or white cells. A diagnosis of thrombocytopenic purpura was made. Several blood transfusions were given and a splenectomy was performed on the fifteenth hospital day. The patient was kept digitalized and made a prompt recovery. After several transfusions the red-cell count rose to 4,300,000. The bleeding tendency ceased, but the platelet count did not rise.

During the third hospital week the patient became hoarse. The hoarseness increased, and on the twenty-ninth hospital day the left vocal cord was found to be completely paralyzed. The temperature following splenectomy had had daily swings from normal to 100 or 101°F.

On the thirtieth hospital day, the temperature spiked to 104°F. and he began to have paroxysms of cough, during which he brought up bloody sputum. There was no pain; the blood pressure was 110 systolic, 60 diastolic, and the respiratory rate was 22. Dullness and diminished breath sounds developed in both lung bases. X-ray examination of the chest showed an extensive area of increased density close to the right side of the dorsal spine, as well as areas of increased density extending into both lung fields, more marked on the left than on the right. This had not been seen on the films taken two days previously. One swallow of barium was given and, before fluoroscopic observation was possible, the patient experienced a coughing spell, following which barium was seen to outline the previously described irregular mass in the esophagus and also the lower end of the trachea and both stem bronchi. A large amount of barium collected in an irregular cavity that was apparently connected with the esophageal mass and not with the bronchus (Fig. 1). The temperature and respirations remained elevated, and the cough became ineffective. On the thirty-sixth hospital day he became semiconscious, coughed and vomited gross blood and finally went into shock and expired.

Differential Diagnosis

Dr. Earle M. Chapman: May we see the x-ray films?

Dr. George W. Holmes: In this set of films there is nothing definite in the lungs or in the appearance of the heart. The esophagus shows no

Figure 1.

obstruction but has a peculiar appearance in the midportion. I do not know when these spot films were taken, but obviously there is a lesion at this point. There is no evidence of disease in the lungs or heart. To go back to the esophagus, there is an extensive filling defect in it, with some dilatation. It is not the annular infiltrating type of lesion that one ordinarily sees but has the appearance that one sees when there is something inside the esophagus, either a lobulated tumor mass or a foreign body, or both. Later on something happened that allowed the barium to pass from the esophagus into the bronchial tree (Fig. 1) and there is quite a different picture, which is now that of a fistula between the esophagus and the bronchial tree.

DR. CHAPMAN: The bronchial tree at the bifurcation lies on the anterior wall of the esophagus. What is the relation of the aorta at this level to these two structures?

DR. HOLMES: They are close to the ascending aorta.

DR. CHAPMAN: It seems to me that this patient died because of a lesion that was located in an area at the level of the bifurcation of the trachea and at the portion of the esophagus that we believe was 29 cm. down from the teeth. At the level of this eroding lesion there were several structures. We have to believe that it involved the trachea, the bronchi at the bifurcation and the anterior wall of the esophagus and the heart; the left and right auricle lie anterior to this, and the ascending portion of the aorta lies immediately behind. What sort of process would first cause trouble in swallowing and later lead to definite erosion? I should like to ask Dr. Holmes why there was no ballooning of the esophagus above the lesion.

DR. HOLMES: The esophageal wall was rigid and did not expand. A cancer can do that; of course there are other more unusual lesions.

DR. EDWARD B. BENEDICT: We see cancer frequently without obstruction and without much dilatation.

DR. CHAPMAN: It seems clear that this man had an eroding process in the esophagus. He was esophagoscoped, and from there on his course was an unhappy one; he went into shock and bled into the intestinal tract and also into the bronchial tree. The incident of cardiac disturbance might well have been from irritation of the sinoauricular node, which lies in the auricle at this same level. The disturbance of rhythm was controlled, and I do not believe that it indicates coronary occlusion.

DR. HOLMES: The descending aorta is seen fairly well, and if one can tell anything from examination of the x-ray films, he did not have an aneurysm of the aorta.

DR. CHAPMAN: If one can tell, but of course one cannot always tell.

DR. HOLMES: I thought it might help you.

DR. CHAPMAN: Many points suggest syphilis rather than carcinoma.

DR. HOLMES: I thought that you were working up to a differentiation of tumors and aneurysm and were assuming that there was more in the x-ray films than there is.

DR. CHAPMAN: I should like to know about the Hinton and Wassermann tests. There are many things that favor syphilis and I might as well discuss that diagnosis. The patient had angina four years before entry, and it cleared up considerably; this is unusual for ordinary angina, it is usually progressive. We are told that he had a blowing diastolic murmur along the left border of the heart. If we can accept that as a fact, it is strong evidence of a syphilitic lesion involving the heart and causing aortic regurgitation. We know that he finally died from a process that eroded through into the bronchus and into the esophagus, so if it were an aneurysm it must have been in the descending aorta, a most unusual place. Is that correct, Dr. Holmes?

DR. HOLMES: Yes.

DR. CHAPMAN: This is likelier, however, to be a tumor. Where, then, did the primary tumor lie? With the x-ray description and the later description that it did not cause obstruction, one wonders if it arose from the heart and penetrated the esophagus, or if it arose at the bifurcation of the trachea or in the bronchial tree and was perhaps growing inward to the anterior wall of the esophagus. A good deal of blood had obviously leaked from the primary tumor into the lungs, and he had pneumonitis when he died. Even the barium, as you see, passed out into the lungs through the eroded area. Primary carcinoma of the esophagus has to be considered.

The appearance of purpura hemorrhagica or thrombocytopenic purpura, I believe, was symptomatic of the other process. Whether the main process was syphilis or carcinoma, it is obvious that splenectomy did not increase the platelets, so probably it was not a true thrombocytopenic purpura, which is followed by a rise in platelets after splenectomy.

What else do we have to consider?

In reading one of the x-ray descriptions I thought of pulmonary infarction because of the linear areas of density, but I do not believe that we have to consider such a diagnosis in this case. The disturbance of cardiac rhythm is interesting. I should guess that this man had a good deal of inflammatory reaction about the heart, which involved the surface of the auricles, and that this irritation set up a disturbance of rhythm.

What types of tumor do we have to consider other than carcinoma? It may be that this man's symptoms four years before entry, interpreted as angina, were mistakenly diagnosed. This assumption is supported by the normal electrocardiogram and by Dr. Holmes's statement that the heart was normal by x-ray. He might have had a benign lesion in the esophagus, such as a polyp, that was causing intermittent obstruction and symptoms simulating angina. The reason he got better is that the trouble was not cardiac or vascular in origin. I wonder if he had some unusual type of tumor, such as a hemangioma. All these are remote, however, and it is up to the pathologist to tell what type of tumor this man actually had. I regret the lack of a blood Hinton test, although I do not believe that the lesion was an aneurysm.

DR. RONALD C. SNIFFEN: There was a negative Hinton test reported in the record, which supports your argument against syphilis.

CLINICAL DIAGNOSIS

Carcinoma of esophagus.

Dr. Chapman's Diagnoses

Mediastinal tumor (? type), involving esophagus, bifurcation of trachea and auricles.
Purpura, symptomatic.

Anatomical Diagnoses

Malignant lymphoma (clasmatocytic type) of esophagus and mediastinal and retroperitoneal lymph nodes.
Esophagobronchial fistula.
Purpura, symptomatic.
Coronary sclerosis.
Operative wound: splenectomy.

Pathological Discussion

Dr. Sniffen: This man had a tumor that surrounded the esophagus, starting at the bifurcation of the trachea and extending downward for 11 cm. The mucosa of the anterior esophageal wall was destroyed over an 11-by-3 cm. area. Tumor also involved the mediastinal lymph nodes and had spread to the right lower lobe, eroding one of the secondary branches of the lower lobe bronchus. In doing this it had produced a fistula between the esophagus and the bronchus, with the result that a 12-cm. abscess had formed in the right lower lobe in its medial part, with satellite abscesses lateral to it. Tumor also involved the retroperitoneal lymph nodes behind the stomach and had ensheathed the arch of the aorta. Microscopic sections of this tumor showed a clasmatocytic lymphoma or, in other words, a reticulum-cell sarcoma.

In addition he had a widespread purpura of the skin, the mucous membranes of the small intestine and kidney pelves and the pancreas. Two hundred centimeters of bloody fluid were found in each pleural cavity, and 100 cc. in the pericardial sac. The heart was not enlarged, but there were ecchymoses in the epicardium, in the endocardium of both ventricles and throughout the muscle of the septum and left apex. He had quite severe arteriosclerosis of the coronary arteries, but we could find no occlusion. The only indication of rheumatic heart disease was slight interadherence of the cusps of the aortic valve. The bone marrow was not involved by tumor; it was hyperplastic and contained only a few megakaryocytes. We know that purpura does occur in a small percentage of people with malignant lymphoma. I am not sure whether or not one has to have bone-marrow involvement to produce the purpura. We could find nothing abnormal in the resected spleen.

CASE 31172

Presentation of Case

A seventy-five-year-old business executive was brought to the hospital after he had collapsed in the street.

He had had frequent medical checkups for the past twenty-five years and until about six months before admission had been active and well, with a blood pressure of 160 systolic, 90 diastolic. At that time he began to notice a feeling of pressure or aching in the upper sternal region during exertion. Four months later the pain was no longer present. During the past few months he had had nocturia (three or four times) and had been treated nonsurgically for prostatic hypertrophy. On the evening before admission he noted a dull ache in the lumbar region of the back. Despite moderate discomfort he fell asleep but noticed the ache when he arose to urinate as usual during the night and when he got up the following morning. He had an unusually small bowel movement that morning and passed urine without difficulty at noon. After breakfast he took a streetcar downtown. After an early noon lunch he walked into the street, whereupon the pain in the back became severe. He felt faint and collapsed, losing consciousness for a period of a few minutes. About ten minutes after he was brought into the hospital he vomited a large amount of gastric content, which contained no gross blood. Approximately half an hour later he vomited again and felt much relieved, although he still complained of slight pain in the back.

Physical examination showed a well-developed, well-nourished man in a state of collapse. The blood pressure was 80 systolic, 60 diastolic. The pulse was 94 and of poor quality. The neck veins were not distended. The apex beat could not be felt, and the heart sounds were very distant. There were no murmurs or gallop rhythm. The lungs were clear, and the abdomen was soft, with slight tenderness in the right lower quadrant; no masses could be felt. The liver and spleen were not palpable. A surgical consultant was impressed by an easily felt pulsation low in the left abdomen. This pulsation lay more laterally than one would expect, unless the aorta were displaced to the left. Good femoral pulsations were felt bilaterally. The dorsalis pedis and posterior tibial arteries could not be felt. The arms and legs were cool.

The oral temperature was 97°F; four hours later the rectal temperature was 100°F. The pulse and respirations did not change significantly.

Examination of the blood four hours after admission showed a white-cell count of 27,600, with 84 per cent neutrophils, 12 per cent lymphocytes and 4 per cent monocytes. Two electrocardiograms taken six hours apart showed no progression of change. Both showed normal rhythm, at a rate of 70 to 80, and marked left-axis deviation. There was slight depression of the ST segments in Leads 2 and 3, and very low T waves in Leads 1 and CF_4, with diphasic T waves in Lead CF_5; QRS was of a low amplitude in CF_3.

The patient lay quietly in bed conversing amiably, in no pain. The pulse was strong. The abdomen

was flaccid, save in the right lower quadrant, where at first he was quite tender. After reassurance there was little spasm and extremely little tenderness. There was a soft, slightly fluctuant, nonpulsating mass, which gave the sensation of mobility that one gets with a large soft cyst or wadded loops of bowel. The easily felt pulsations low in the left abdomen were still present. Peristalsis was normal. He continued to have pain in the back and noted a slight pain down the anterior aspect of the right thigh. Shortly after the examination the patient suddenly sat up in bed, gasped and expired.

Differential Diagnosis

Dr. Robert R. Linton: The blood pressure was 160 systolic, 90 diastolic. That sounds like a fairly good blood pressure for a man of this patient's age. What do you think, Dr. Richardson?

Dr. Wyman Richardson: It is an excellent blood pressure.

Dr. Linton: It seems to me that I have to decide why this man went into shock as he walked out into the street and, after a period of relatively few hours, suddenly died. I can think of four conditions that might explain his demise. Certainly something quite dramatic happened, as evidenced by his losing consciousness and the reduction in blood pressure after admission to the hospital. I cannot get much reliable information from the physical examination, and I wonder what this questionable mass was that they thought pulsated in the left side of the abdomen.

Did this man have an aneurysm of the abdominal aorta? From the physical examination described here, I should say that he did not, unless the aneurysm had ruptured, producing a large hematoma in the retroperitoneal tissues. Even if he had that, I think that one would still be able to feel the original abdominal aneurysm. He could have had a slow leak from it and succumbed.

Another possibility is that he had pulmonary embolism. I doubt very much that he died from embolism since he had been walking around until shortly before death. It is most unusual for patients who have been ambulatory to develop a massive fatal pulmonary embolism; they may have minor pulmonary infarcts.

Did he die of coronary heart disease? That is a question which I cannot answer, and I should like someone to interpret the electrocardiograms.

Dr. Conger Williams: I took both electrocardiograms, so I shall simply say that I found no difference between the two films. I was able to conclude only that the changes were probably of long standing.

Dr. Linton: Are they consistent with coronary heart disease?

Dr. Williams: Consistent with, but not diagnostic of, infarction — that is the way I expressed it.

Dr. Linton: I do not see how we can connect up the heart with the pain in the back and the abdomen, so far as coronary heart disease or cardiac infarction is concerned. But there is one other condition that ought to be seriously considered. Did he have a dissecting aneurysm of the arch of the aorta? I do not know any positive way of making that diagnosis. If he had had absent pulsations in the arteries to the lower extremities I should more seriously consider such a diagnosis. The patients whom I have seen have had diminution or absence of pulsations in the lower extremities owing to the fact that the blood had dissected down the layers of the aorta and had gradually shut off the arterial flow.

I cannot think of any other possibility that might explain the sudden demise, and I favor the diagnosis of an abdominal aneurysm that had ruptured, with the patient dying as a result.

Dr. Williams: When this patient came in it was obvious that he had some sort of very severe accident, which we thought was vascular. The diagnosis of dissecting aneurysm was considered as time went on. The pulse was almost imperceptible when he came in, but between examinations the pulse gradually increased in strength. The blood pressure nevertheless stayed fairly low, which may have interfered with the pulsation of the mass in the abdomen. As a result of the dilatation in the aorta the cardiac output was very poor. It is interesting that the mass in the abdomen was not visible on the previous evening. The next morning, when we were visiting and stopped outside to discuss the sudden appearance of the mass, the patient died in a period of about thirty seconds.

Dr. Richardson: I should like to mention that everything points to the fact that this man had severe hemorrhage. Might it have been within the bowel, an unrecognized ulcer or something else. The mass felt might have been due to a large amount of blood in the bowel that had not been passed. Is that possible?

Dr. Linton: Most patients with massive gastric hemorrhage vomit the blood or pass it by rectum.

Dr. Richardson: Most of them do, but I have seen some that did not.

Dr. Linton: Another thing, he vomited but he did not vomit blood. I believe that the vomiting was secondary to vagus stimulation.

Dr. Richardson: Owing to blood in the abdominal cavity?

Dr. Linton: Yes; blood in the region of vagal distribution — in the retroperitoneal area.

A Physician: How about pain in the back?

Dr. Linton: It seems to fit abdominal aneurysm more than anything else. One might think of acute pancreatitis, but people do not die so suddenly from acute pancreatitis.

Dr. Richardson: I was thinking of acute ulcer with hemorrhage.

Dr. Benjamin Castleman: A factor against dissecting aneurysm is the fall in blood pressure, which usually remains elevated. With a dissecting aneu-

rysm extending down into the abdominal aorta, dissection almost always extends into the iliac arteries as well and there should be a diminution in the pulse in the legs, as Dr. Linton has intimated.

Dr. Williams: Another point against it is the level of the blood pressure before this happened; it was 160 systolic, 90 diastolic, which is not remarkable. These patients usually have a higher blood pressure, although it has been reported in those with normal blood pressures.

Clinical Diagnosis

Mesenteric thrombosis?

Dr. Linton's Diagnosis

Ruptured abdominal aortic aneurysm.

Anatomical Diagnoses

Arteriosclerotic aneurysm of abdominal aorta, with rupture.
Retroperitoneal hematoma, right.
Coronary sclerosis.
Myocardial fibrosis.
Cardiac hypertrophy.

Pathological Discussion

Dr. Castleman: This man had a large arteriosclerotic aneurysm of the aorta beginning below the origin of the renal artery and extending down to the bifurcation. The aneurysm in places had a circumference of 18 cm. It had ruptured on the right side through a large linear tear 8 cm. in length. This tear was undoubtedly the terminal episode; the first attack was probably a small rupture with a slow leak, which accounts for the huge retroperitoneal hematoma that was felt just before he died. The aneurysm was arteriosclerotic, there being no evidence to suggest syphilis. Both common iliac and right hypogastric arteries were also markedly dilated — the diffuse aneurysmal dilatation not infrequently seen with severe arteriosclerosis. The heart was moderately enlarged, weighing 452 gm. There was evidence of severe coronary sclerosis and myocardial fibrosis.

Dr. Linton: I wonder when he had had his most recent clinical checkup. He was supposed to have had them frequently.

Dr. Williams: He was a rather heavy-set man, and it is quite possible his physician would not have been able to feel the aneurysm.

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PENICILLIN IN BACTERIAL ENDOCARDITIS

Prior to the introduction of the sulfonamides, medical science possessed no effective agent for the treatment of bacterial endocarditis. Sulfonamide therapy constituted a tremendous advance in the management of this disease by demonstrating for the first time that bacterial endocarditis could be cured, but its usefulness proved to be disappointingly limited. The various sulfonamide derivatives had little or no effect on cases of acute bacterial endocarditis, and less than 5 per cent of patients with the subacute form of the disease were permanently benefited by their administration; thus, it soon became clear that an even more effective chemotherapeutic agent was needed. Surgical treatment, although sometimes successful in patients in whom infection is superimposed on a patent ductus arteriosus, unfortunately offers nothing to the majority of patients with bacterial endocarditis.

Good evidence to the effect that penicillin is a potent agent for the treatment of this disease is beginning to accumulate.[1–3] Further support for this view is to be found in the work of Meads, Harris and Finland, reported elsewhere in this issue of the *Journal*. Of 10 patients with subacute bacterial endocarditis treated with penicillin during 1944, at the Boston City Hospital, 7 had the infection arrested, at least temporarily; and 3 of 7 patients with acute bacterial endocarditis are likewise reported to be well. The results in this relatively small series are in close agreement with those in a much larger group that have been reported to the Committee on Chemotherapeutics and Other Agents of the National Research Council. These reports indicate that, in cases in which the infecting organism was sensitive to the action of the drug, penicillin therapy arrested the infection in 55 to 60 per cent of cases of subacute bacterial endocarditis and in 25 to 40 per cent of cases of acute bacterial endocarditis caused by pyogenic cocci. To accomplish these results, it was necessary to administer not less than 200,000 units of penicillin daily for two or more weeks. When used alone, penicillin was fully as effective as when given in conjunction with an anticoagulant. Thus, the simultaneous administration of heparin or dicumarol appears to be neither necessary nor desirable.

In cases of either subacute or acute bacterial endocarditis in which the infecting organism was shown to be resistant in vitro to the action of penicillin, even extremely large doses of the drug had no effect. It has been recommended, therefore, that before or at the beginning of therapy the causative organism in each case be tested for its susceptibility to penicillin. This procedure is especially indicated in cases of subacute bacterial endocarditis caused by nonhemolytic streptococci. Although most strains of this type of streptococcus are sensitive to penicillin, occasional ones with a high natural resistance to the drug are encountered.[4]

There can be no question that penicillin is the most effective agent now known for the treatment of bacterial endocarditis. It is still too early to estimate in what percentage of cases actual cure of the disease is obtained. Follow-up observations of a year or even longer are needed before the fact of cure can be established. As indicated by the experience at the Boston City Hospital, relapse or reinfection may occur several months after the apparent successful completion of treatment.

Bacterial endocarditis remains a serious disease, and the search for an even more efficient form of therapy will no doubt continue. It is clear, however, that the physician now has at his command an agent that gives promise of curing upward of half the patients suffering from this disease. The early diagnosis of bacterial endocarditis thus becomes a problem of practical importance, as well as one of academic interest.

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4. Dawson, M. H., Hobby, G. L., and Lipman, M. O. Penicillin sensitivity of strains of non-hemolytic streptococci isolated from cases of subacute bacterial endocarditis. *Proc. Soc. Exper. Biol. & Med.* **56**:101, 1944.

MAY DAY AND BIRTH REGISTRATION

The first day of May has been set aside as Child Health Day in this country since 1923, a new tradition that was officially sanctioned by Congress in 1928. Its observance is now dignified further through the recognition accorded it by the American Child Health Association, state and provincial health authorities and the Children's Bureau of the United States Department of Labor. In our busy cycle of duties, and of observances and performances, we have fittingly set aside one day each year on which to give thought to the onrushing generations.

It has been customary, in this observance of Child Health Day, to feature some particular point deserving emphasis — the health of young workers in 1943 and immunization against diphtheria and smallpox in 1942. This year, when masses of persons in other, less fortunate, countries have lost their social security and practically their personal identities, the importance of birth registration has been selected as the May Day feature story.

The significance to everyone of birth registration and the birth certificate is so obvious as hardly to need elaboration. Suffice it to say that it furnishes incontrovertible evidence of one's identity, and on it may depend the right to an education and the right to work, to vote, to marry or to enter civil service. Various other civil rights may hinge on this proof of age and of citizenship — obtaining an automobile license or a pilot's license, Social Security benefits and the settlement of pensions. On this evidence of birth may also depend the proof of parentage and of legal dependency, the inheritance of property and the settlement of insurance.

The registration of births is an obligation that falls almost entirely on the attendant at the birth, which, in this state, ordinarily means the physician. Massachusetts stands well in its record of birth registrations, ranking, with its total percentage of 98.9, high among the twenty-eight states and the District of Columbia with registrations of 95 per cent and over. In this it is surpassed, in fact, only by Connecticut, New Jersey and Minnesota. Among the less adequately registered southern states, Arkansas trails, with a percentage of 75.9.

A registration percentage of 98.9 is good, although it can and should be better. When we realize that, in the Nation, since the attack on Pearl Harbor about 700,000 babies have been born who are still unregistered, we become aware of a figure that we can face less complacently.

MASSACHUSETTS MEDICAL SOCIETY

Treasurer's Report Covering Distribution of Refund

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to district societies for 1944:

The Council voted to distribute the sum of $4000 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 3297. The refund to the district societies for each paid fellow is therefore $1.213.

The following table gives the number of payments, as of March 1, and the refund to each district as of April 3:

District	Number Reported Paid	Refund
Barnstable	32	$38.87
Berkshire	88	106.78
Bristol North	45	54.63
Bristol South	139	168.64
Essex North	128	155.30
Essex South	191	231.72
Franklin	31	37.65
Hampden	210	254.76
Hampshire	49	59.48
Middlesex East	83	100.74
Middlesex North	80	97.08
Middlesex South	661	801.83
Norfolk	587	712.06
Norfolk South	93	112.86
Plymouth	98	118.92
Suffolk	442	536.18
Worcester	275	333.61
Worcester North	65	78.89
	3297	$4000.00

In 1944, for comparison, the total number of payments for the refund was 3060.

ELIOT HUBBARD, JR., M.D., *Treasurer*

DEATH

KNOWLTON — Charles D. Knowlton, M.D., of Rockport, died January 5. He was in his seventy-eighth year.

Dr. Knowlton received his degree from Tufts College Medical School in 1894. He later studied at the University of Pennsylvania School of Medicine and at the University of Berlin. He was formerly assistant professor of theory and practice of medicine at Tufts College Medical School and instructor in laryngology at Harvard Medical School. He was a consulting surgeon at the Massachusetts Eye and Ear Infirmary and was formerly president of the Norfolk District Medical Society. He was an affiliate fellow of the American Medical Association.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

FLANDERS — Louis W. Flanders, M.D., of Dover, died January 16. He was in his eighty-first year.

Dr. Flanders received his degree from the University of Vermont College of Medicine in 1885. He was a member of the Strafford County Medical Society and the New Hampshire Medical Society. He was a past president of the New Hampshire Medical Society.

His widow, a son, two sisters and a brother survive.

WESTON — Arthur F. Weston, of Keene, died March 23. He was in his seventy-third year.

Dr. Weston received his degree from Boston University School of Medicine in 1903.

His widow, a daughter and a sister survive.

MISCELLANY

ANNUAL PRIZE SUBSCRIPTION

The annual prize subscription offered by the *New England Journal of Medicine* for the best undergraduate contribution to the *Tufts Medical Journal* has been awarded to A. Harvey Salans, '46, for his paper "Rheumatic Fever: A major public-health problem," which appeared in the June, 1944, issue. The paper "Penicillin: A review," by Henry H. Banks, '46, received honorable mention; it appeared in the April, 1944, issue. According to custom, these students will be given a two-year and a one-year subscription to the *Journal*, respectively.

CORRESPONDENCE

SCHOOL PHYSICIANS

To the Editor: When any medical journal prints an editorial in which the school physician is even mentioned, that event becomes front-page news.

The editorial in the March 15 issue of the *Journal*, concerning the Strayer survey, had some pertinent things to say about school health programs in general. Every experienced school physician will agree with the statement that health service "suffers from overdetailed legal prescriptions and inferior physical equipment." One of the reasons, perhaps the greatest one, for this situation is the attitude of organized medicine. The position of school physician is a legitimate specialty in medicine, but it has never been recognized as such by the Massachusetts Medical Society. The school physician is the only member of the school staff whose basic training qualifies him to head up the school health program. If organized medicine fails to give public recognition and professional support to this work, how can we expect city and town officials to provide adequate financial support for it?

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DIAGNOSTIC TEST DOSE OF NEOSTIGMINE

On page 289 of the March 8 issue of the *Journal* mention is made, in the discussion of one of the case records of the Massachusetts General Hospital, of the neostigmine (Prostigmin) test for myasthenia gravis. The dose used for this test is given as 0.5 mg. of neostigmine methylsulfate by intramuscular injection. This is not sufficient when the drug is to be used as a diagnostic test in an adult. The matter of dosage was pointed out by Schwab and myself (Schwab, R. S., and Viets, H. R. Prostigmin test in myasthenia gravis. *New Eng. J. Med.* **219**:226-228, 1938), 1.5 mg. of neostigmine methylsulfate being advised. Since that time, a special diagnostic ampule has been put on the market; this contains 1.5 mg. of neostigmine methylsulfate and 0.6 mg. of atropine sulfate. In order to avoid a false, negative or incomplete report, the dosage contained in the diagnostic ampule is recommended.

HENRY R. VIETS, M.D.

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Boston 14

A PLEA FOR MIDDLESEX

To the Editor: The editorial "Standards of Medical Education" in the February 1 issue of the *Journal* was quite interesting. I, too, am one of those whose photograph is represented by the historic picture taken when Governor James M. Curley signed that bill. Let us be fair and reasonable. So long as the Commonwealth of Massachusetts has chartered a medical school and recognized the graduates, is it logical to recognize graduates from other states when those states refuse to recognize all graduates from Massachusetts? There are several states which refuse to recognize graduates from other states because the latter discriminate by failing to give recognition to graduates of the former, for example, Ohio, New York and Connecticut. Why does not Massachusetts protect its own graduates?

There are a few hundred graduates from Middlesex University School of Medicine who are fellows of the Medical Society; there are many commissioned officers in the armed forces from Middlesex; there is a graduate from Middlesex who is medical examiner appointed by former Governor Saltonstall; a graduate from Middlesex was appointed to the United States Public Health Service; there is a health officer in one of the neighboring cities of Boston who is a Middlesex graduate; many Middlesex graduates completed their internships in some of the finest hospitals; many Middlesex graduates are in active practice; several Middlesex graduates are on the staffs in a few hospitals in the Commonwealth; and there are several Middlesex graduates practicing in other states. Yet, in spite of all this, graduates from Middlesex are discriminated against in hospitals, in appointments and even at the present time in the armed forces. When they entered on the study of medicine, they had all the necessary requirements; they completed the prescribed courses, as per law; they received their M.D. degrees; they underwent their required internships; and they passed the medical licensing examinations. Still, they are not given the

same opportunity as other graduates. It is a shame to penalize such qualified graduates.

Middlesex is showing that she is willing to do everything that is humanly possible to improve the medical school in order to get recognition. Why does not the Massachusetts Medical Society, which is playing such a vital part, and the Approving Authority and the American Medical Association do everything possible to help Middlesex? I can name medical schools which were not given full recognition by the New York State Board of Regents but which, with the proper help, did receive recognition. Unless complete cooperation is shown to help Middlesex become as good a medical school as any other, I firmly feel that the General Court should pass legislation to eliminate the Approving Authority and should also pass laws forbidding recognition to graduates from other states that refuse to recognize all graduates from our medical schools. If full recognition in all hospitals were given to its graduates, other states would follow suit.

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NOTICES

BOSTON DISPENSARY

A clinical staff meeting of the Boston Dispensary will be held at the Pratt Hospital Auditorium on Friday, May 4, at 12:30 p.m. Dr. Daniel L. Lynch will speak on the subject "Rehabilitation Problems in Industry." Luncheon will be served at 12 noon.

SUFFOLK DISTRICT MEDICAL SOCIETY

A dinner meeting of the Suffolk District Medical Society will take place on Saturday, April 28, at 7 p.m., at the Harvard Club of Boston. Surgeon-General Thomas Parran, of the United States Public Health Service, will speak on the subject "Place of the Hospital in Postwar Medical Care." Tickets $3.75.

TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet in the Auditorium of the Beth Israel Hospital, Boston, on Wednesday, May 9, at 8:15 p.m. Dr. Fuller Albright will speak on the subject "Action of Vitamin D."

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, May 2 — The Spleen, the Bone Marrow, and Thrombopenic Purpura. Dr. William Dameshek.

Friday, May 4 — The Heart in Hypertension since the Days of Richard Bright. Dr. Paul D. White.

Wednesday, May 9 — Cardiac Clinic. Dr. Heinz Magendantz.

Friday, May 11 — Carcinoma of the Prostate. Dr. William C. Quimby.

Tuesday, May 15 — Clinicopathological conference. Drs. Chester S. Keefer and H. E. MacMahon.

Wednesday, May 16 — Endocrine Problems in Childhood. Dr. Richard Wagner.

Friday, May 18 — Thyroid Disease. Dr. Frank H. Lahey.

Wednesday, May 23 — Common Duct Stone: A review of cases. Dr. William T. Roberts.

Friday, May 25 — Peri-Arteritis Nodosa and Acute Disseminated Lupus from the X-ray Viewpoint. Dr. Merrill Sosman.

On Monday mornings (except May 7) clinics will be given by Dr. Samuel Proger. On Tuesday and Thursday mornings Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings clinics will be given by Dr. William Dameshek.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, May 3, in the classroom of the nurses' residence.

PROGRAM

Laryngotracheobronchitis: Brief summary of six cases having penicillin treatment. Drs. Helen N. Perry and Clara Waldinger.

Bacteriological Observations and Local Use of Penicillin. Miss Anita B. Mangiaracine.

Discussion of nasal drops.

Dr. Margaret Noyes Kleinert will be chairman.

EDWARD K. DUNHAM LECTURES

The Faculty of Medicine of Harvard University has announced that the following lectures on the general topic "The Insect as a Medium for the Study of Physiology" will be delivered by Dr. Vincent B. Wigglesworth under the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences:

Monday, May 7. The Insect Cuticle as a Living System.

Wednesday, May 9. Hormones and the Regulation of Insect Growth.

Friday, May 11. Integration in the Epidermis of Insects.

These lectures are scheduled for 5 p.m. at the Harvard Medical School, Building C Amphitheater.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 3

FRIDAY, MAY 4

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Mallory Building, Boston City Hospital.

SATURDAY, MAY 5

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, MAY 7

*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, MAY 8

*9:00–10:00 a.m. Medical clinic. Infants' Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, MAY 9

*12:00 m. Clinicopathological conference. Children's Hospital.

*12:00 m.–1:00 p.m. Clinicopathological conference, Cambridge Hospital.

*Open to the medical profession.

APRIL 28. Suffolk District Medical Society. Notice elsewhere on this page.

APRIL 30. New York Institute of Clinical Oral Pathology. Page 334, issue of March 15.

MAY 2–25. Joseph H. Pratt Diagnostic Hospital. Medical conference program. Notice elsewhere on this page.

MAY 3. New England Hospital for Women and Children. Notice elsewhere on this page.

MAY 4. Boston Dispensary. Notice elsewhere on this page.

MAY 7, 9 and 11. Edward K. Dunham Lectures. Notice elsewhere on this page.

MAY 9. Tufts Alpha Omega Alpha. Notice elsewhere on this page.

MAY 10. Advances in Obstetric Technics. Dr. Roy J. Heffernan. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JUNE 14–19. American Board of Obstetrics and Gynecology. Page 364, issue of March 22.

SEPTEMBER 17. American Public Health Association. Page 752, issue of November 30.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

MAY 17. Lakeville Sanatorium, Lakeville. 11 a.m.

WORCESTER

MAY 9. Annual meeting.